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RESEARCH ARTICLE

SYNTHESIS MEDICINAL IMPORTANCE AND MECHANISTIC STUDIES OF SOME CHROMEN-2-ONE DERIVATIVES AND ALLIED DI-KETO COMPOUNDS

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ABSTRACT

Dicoumarol (3) obtained from 4-hydroxy coumarin (2) through different routs has been found pharmacologically active and responsible for anticoagulant properties. Mechanistically interesting 2-nitroso-2-methyl-1,3-indandione dimer (11) has been synthesized by the nitration of 2-methyl-1,3-indandione (9) when the reaction is carried out at 0^0C. In a patent work phthalimide derivatives (13) synthesized from the reaction of phthalimide with hydrazones have been found to be potent insecticides. Phthalimide esters of the type (14) have also been synthesized and evaluated as potential prodrugs. In a substitution reaction 1H –isoindole-1,3-(2H) dione (12) replaces chloride from chloroacetonitrile to yield N-cyanomethyl phthalimide (15).

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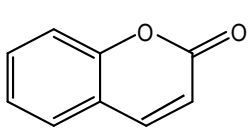
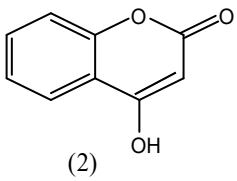
INTRODUCTION

4-hydroxy coumarin, an enol, has been synthesized from chromen-2-one by a hydroxyl group substitution at position-4. Dicoumarol, a derivative of 4-hydroxy coumarin can be synthesized by the reaction of 4-hydroxy coumarin with different reagents under varying conditions. A series of 2-substituted 1,3-indandione derivatives have been obtained either directly from 1,3-indandione or from C-2 alkyl (aryl) substituted 1,3-indandione derivatives. (Kunz.F.J.et.al;1960; Strakov.Y.A,et.al,1996; Aldersley.F.M,et.al,1983). Interesting mechanism for different N-substituted phthalimide derivatives of pharmaceutical interest has also been developed .In this theoretical article author has highlighted the medicinal importance of some known compounds and simultaneously proposed mechanisms for various compounds which were not known earlier as revealed by exhaustive literature survey.

General Discussion: 4-hydroxy coumarins (2), are a class of vitamin K antagonist anticoagulant drug molecules derived from chromen-2-one (1) .Although 4-hydroxy coumarin, itself is not an anticoagulant, it is an important fungal metabolite from the precursor coumarin (1). Dicoumarol (3) present in sweet clover (Melilotus species),is an important derivative of 4-hydroxy coumarin. Dicoumarol having anticoagulant properties, has been biosynthesized non-enzymatically by the reaction of formaldehyde with 4-hydroxy coumarin (Bye *et al.,* 1970) or condensing formaldehyde with 2 equivalents of

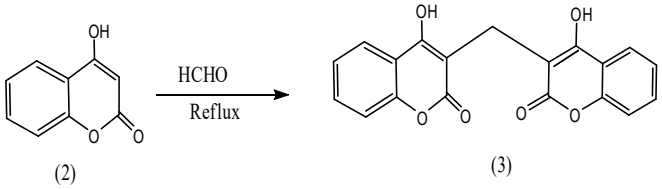


(1)

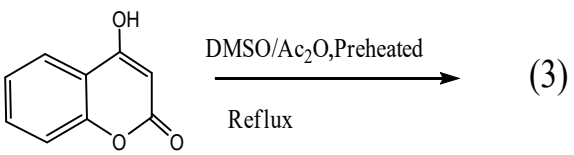


(2)

4-hydroxy coumarin. In a modified work it has also been synthesized by refluxing 4-hydroxy coumarin with pre-heated Dimethylsulphoxide-acetic anhydride reagent at elevated temperature (Khan *et al.,* 1983).

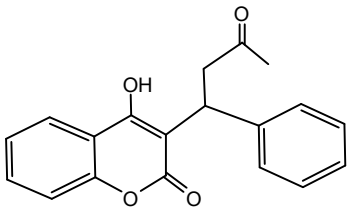


(2) (3)



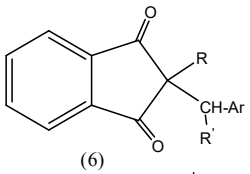
(2) (3)

Warfarin (4), a derivative of 4-hydroxy coumarin is the most studied and commonly used anticoagulant.



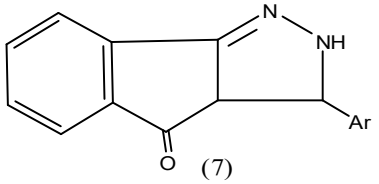
(4)

1,3-indandione (5), an important member of class of 1,3-diketo compounds has been used as a substrate in a series of reactions. A wide range of compounds of both medicinal and chemical importance have been synthesized from this substrate with different reagents under varying conditions. 2-arylidene-1,3-indandiones show addition reactions across the olefinic double bond with secondary amines like piperidene and morpholine to give the corresponding adduct (6). However, the addition reaction with hydrazine and subsequent dehydration affords a different adduct (7). These adducts have been found to have bactericidal and fungicidal activity (Ablak, 1992).



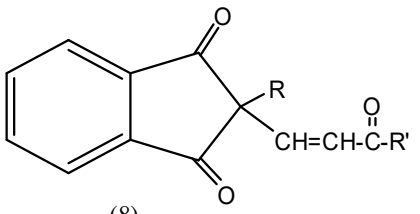
(6)

R=H,R'=-NR_2



(7)

A range of pharmacologically active compounds (8),having anticoagulant, antispasmodic, analgesic and narcotic properties have been synthesized through the reaction of 2-substituted 1,3-indandione with β-chloro-vinyl ketones (Belyaev *et al.,* 1967).

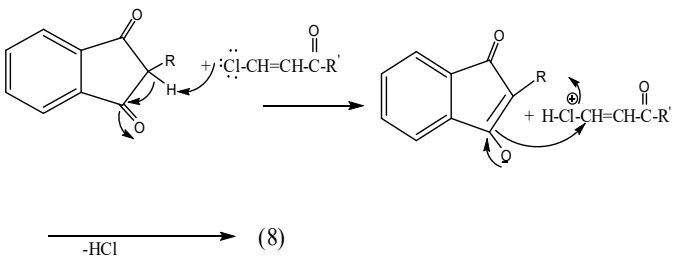


(8)

R=Ph,Me etc.

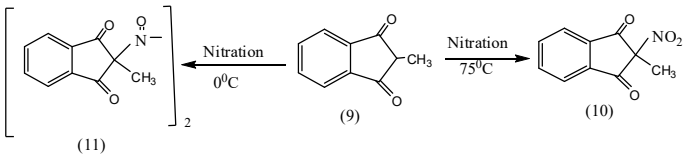
R'=Ph,$PhCH_2$,Pr,p-ClC_6H_4

The plausible mechanism proposed for the formation of (8) can be depicted as below Scheme-1.



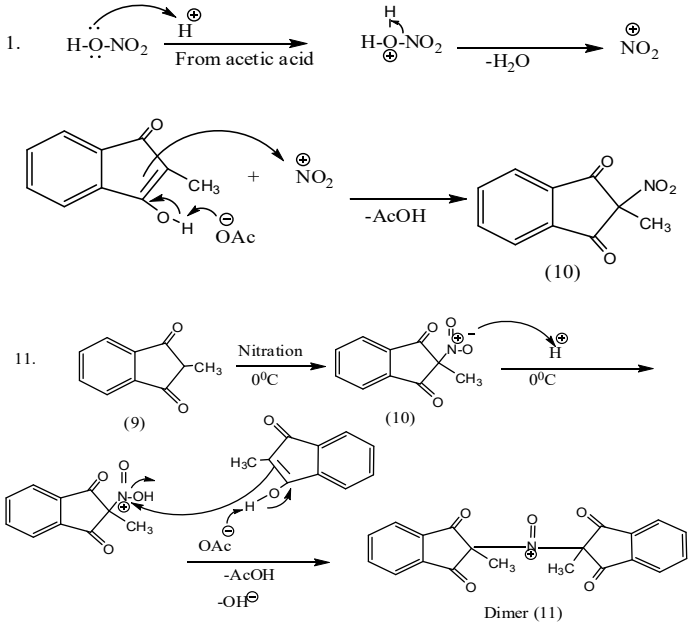
Scheme-1

In a mechanistically interesting reaction, nitration of 2-methyl-1,3-indandione (9) with fuming nitric acid in acetic acid has been carried out at around 75^0C to afford 2-nitro-2-methyl 1,3-indandione (10), however, when the same reaction was carried out below 0^0C, 2-nitroso-2-methyl-1,3-indandione dimer (11) was the final product (Dumpis *et al.,* 1961).



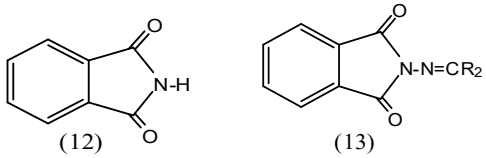
(11) (9) (10)

Mechanism proposed for the products (10) and (11) can be rationalized as under Scheme-2.



Scheme-2

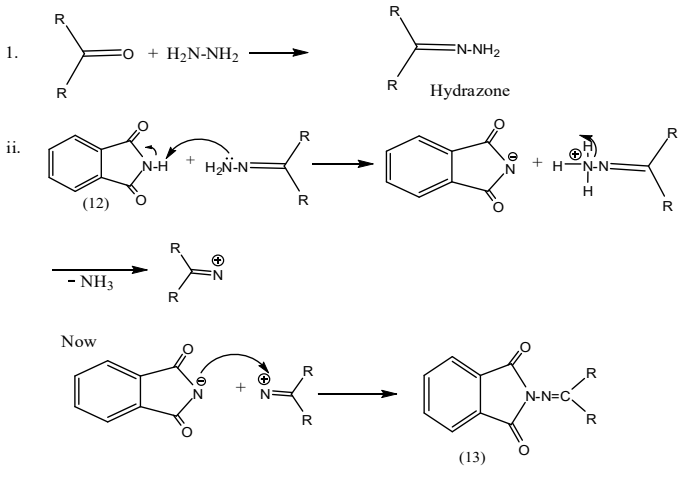
Phthalimide (12) is another important member of class of 1,3-di-keto compounds. Phthalimide derivatives (13) synthesized from the reaction of phthalimide with hydrazones have been found to be potent insecticides (Ebihara *et al.,* 1996).



(12) (13)

Mechanistically the formation of (13) can be shown as below –

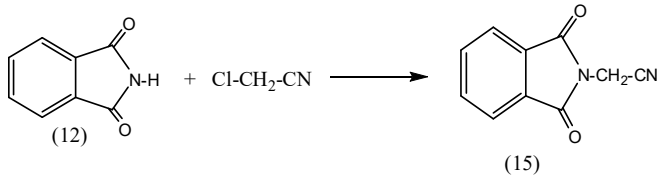
Scheme-3.



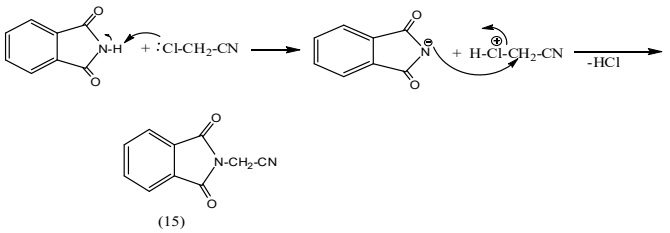
Scheme-3

Phthalimide esters of the type (14) obtained by the reaction of some nonsteroidal anti-inflammatory carboxylic acid drugs with N-hydroxy methyl-phthalimide, have been evaluated as potential pro-drugs with the aim of depressing the gastrotoxicity of the parent drugs.

In a mechanistically interesting substitution reaction 1H – isoindole-1,3-(2H) dione(12) replaces chloride from chloroacetonitrile to yield N-cyanomethyl phthalimide (15).



The plausible mechanism proposed for the formation of (15) can be depicted as below-Scheme-4.



Scheme 4.

Conclusion

Different pharmacologically active enolic compounds and C-2 substituted 1,3-di-keto adducts have been frequently synthesized and have found a wide range of applications in industry, biology, pharmacy and material science. They can also be used as substrates in different reactions under varying conditions using specific reagents and the products so obtained, can be of immense medicinal importance.

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