

Studies on mechanism of formation of 2-substituted-1,3-indandiones/ortho thio quinones and allied heterocycles

Noor ud Din Zargar^{a*} and Khaliq ud Zaman Khan^b

^a Department of Chemistry University Of Kashmir Srinagar (190006) J&K India

^b Department of Chemistry University Of Kashmir Srinagar (190006) J&K India

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ABSTRACT

Ketovinylation of 2-substituted 1,3-indandiones has been achieved by the condensation of Na or K salts of 2-(R-substituted) 1,3-indandione with beta-chlorovinyl ketones to get pharmacologically active 2-(R'-substituted)-1,3-indandiones (**1**). Interaction of 1,3-indandione with tetra cyano ethylene in ethanol gives 2-dicyano methylene compound (**2**) in excellent yields. Ortho hydroxy thio phthalimides (**3**) generate the corresponding ortho thio quinones (**4**) which have been utilized to prepare the heterocycles of potential biological activity. Acetyl and cinnamoyl indandiones (**9**) (R=Me, CH=CHPr) react with aminozoles such as 3-amino-1,2,4-triazole and 2-aminobenzimidazole and afford mechanistically interesting indenoazolo-pyrimidines (**10**) and (1,3-dioxo-indan-2-yl)-azolopyrimidines (**11**) respectively.

1. Introduction

1,3-indandione, an important member of class of β -diketo compounds, has been found to yield a series of compounds of both pharmacological and chemical importance [1-3].

It affords 5-bromo furfuryl diindandionyl-methane with 5-bromo furfural in ethanol [4], and furnishes a condensation product with indazoladione [5]. Reaction of 1,3-indandione with active methylene compounds such as malononitrile has been found to give a variety of compounds. Its condensation with heteroatom carbaldehydes has been reported to give 2-alkylidenes which undergo Michael addition of 1,3-indandione to yield a 2:1 adduct [6].

Nitrogen heterocycles or allied nitrogen containing ring compounds have also been used as substrates in different reactions.

Synthetically useful N-alkoxy phthalimide derivatives have been conveniently prepared in high yields from the reaction of N-hydroxy phthalimide with alkyl halides using DBU in DMF [7]

and N-methyl phthalimide has been obtained by the methylation of potassium salt of phthalimide with dimethyl sulphate [8]. N-hydroxy methylation of phthalimide has been achieved by refluxing it with formaldehyde [9].

In an interesting ring expansion reaction N-(2-aryl-ethyl)-phthalimides undergo photoinduced cyclisation to give 4-aryl-2-benz azepine-1,5-dione [10].

A convenient method for the enantiospecific synthesis of optically active aliphatic sulphenyl chlorides and thio phthalimides has also been reported [11]. Several Mannich base N-mustards have also been synthesized by the condensation of 3-substituted phthalimides and 4-substituted phthalimides with N-bis(-2-chloro ethyl)-amine in ethanol formalin [12].

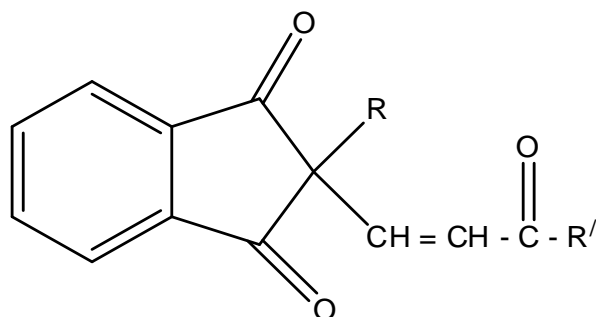
In this article authors have highlighted the biological activity of some compounds and simultaneously suggested/proposed a series of mechanisms for different compounds which were not known or developed earlier.

* Corresponding author. e-mail: nded.1092@rediffmail.com

2. Results and Discussion

1,3-indandione has been used as a model substrate in a wide range of reactions. Potentially anticoagulant or antispasmodic 2-(benzyl,Pr.substituted)-1,3-indandiones (**1**) have been synthesized by the

condensation of Na or K salts of 2-(Ph-substituted) - 1,3-indandione with beta-chlorovinyl ketones of formula $\text{Cl}-\text{CH}=\text{CH}-\text{CO}-\text{R}'$.



Figure;1

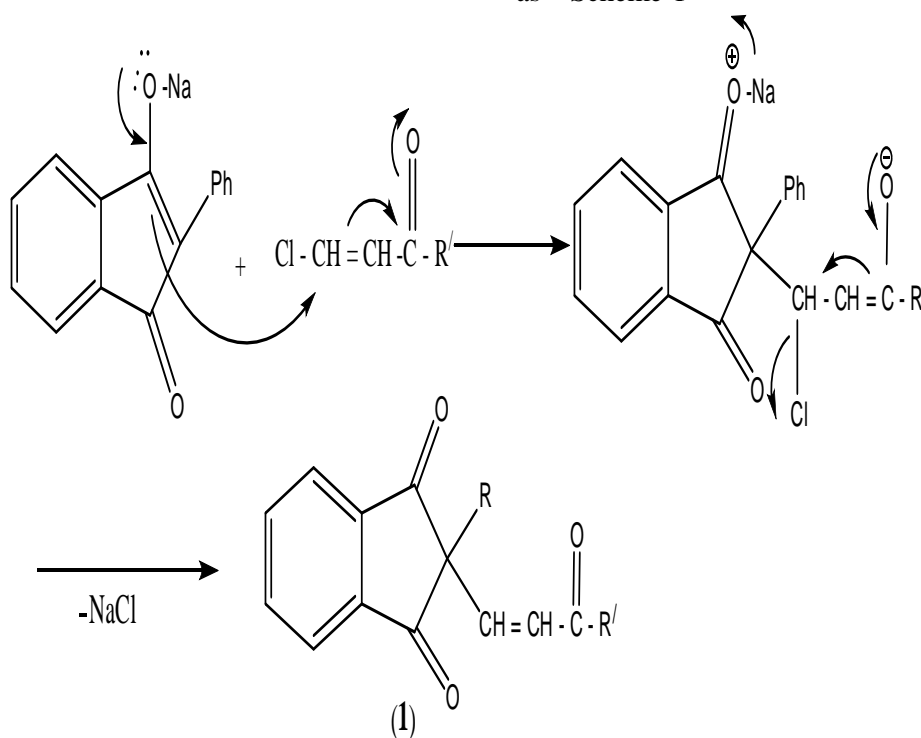
$\text{R} = \text{Ph, Me, etc}$

$\text{R}' = \text{PhCH}_2, \text{Pr, p-Cl-C}_6\text{H}_4 \text{ etc.}$

A suspension of 0.4 g Na in 50 ml xylene and 4 g of 2-(Ph-substituted)-1,3-indandione was heated to 120°C to obtain Na salt as red precipitate. The mixture was cooled to $\sim 0^\circ\text{C}$ and a solution of 3g of beta-chloro vinyl

ketone ($\text{R}' = \text{Ph}$) in 10ml xylene was added during 30 minutes. The mixture was stirred for 2 hrs at $90-100^\circ\text{C}$. Workup of the mixture afforded (**1**) in excellent yields, m.p 141°C .

Mechanistically the formation of (**1**) can be discussed as – Scheme-1



Scheme -1 Proposed mechanism for the formation of (**1**)

In a mechanistically interesting reaction 2-dicyano methylene-1,3-indandione(**2**) has been synthesized by

the reaction of 1,3-indandione with tetra cyano ethylene in ethanol.

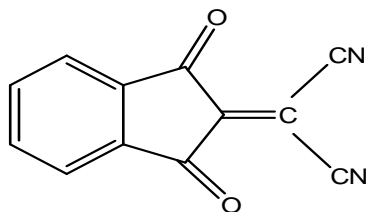
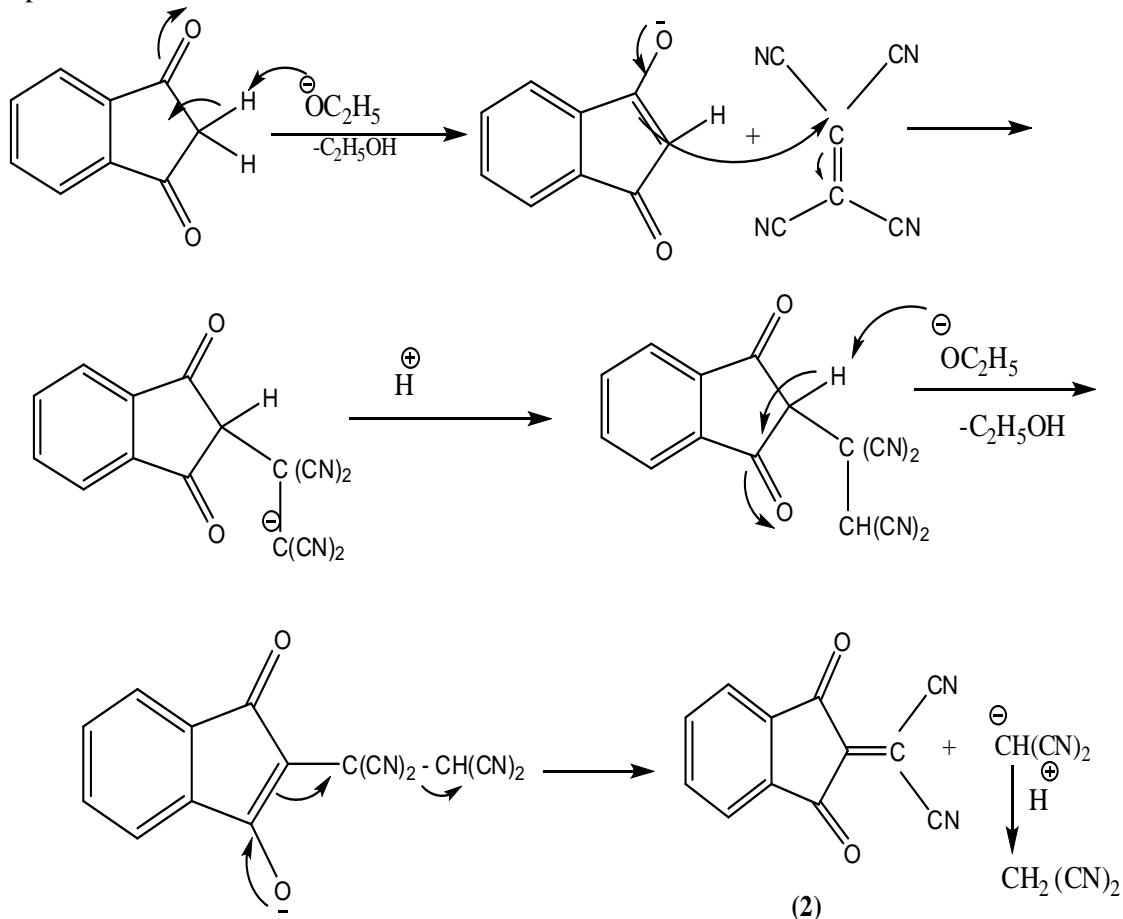


Figure:2 2-dicyano methylene-1,3-indandione

Plausible mechanism proposed for the formation of (2) can be depicted as- Scheme-2.



Scheme-2 Suggested pathway for the formation of (2)

Ortho thio quinones (4), a new class of versatile reactive intermediate dienes, generated from ortho

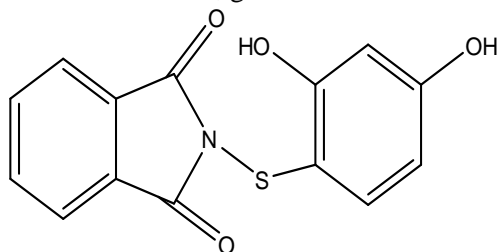


Figure:3 Ortho hydroxy thio phthalimide

hydroxy thio phthalimides (3), have been utilized to prepare heterocycles of potential biological activity.

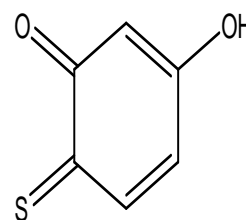
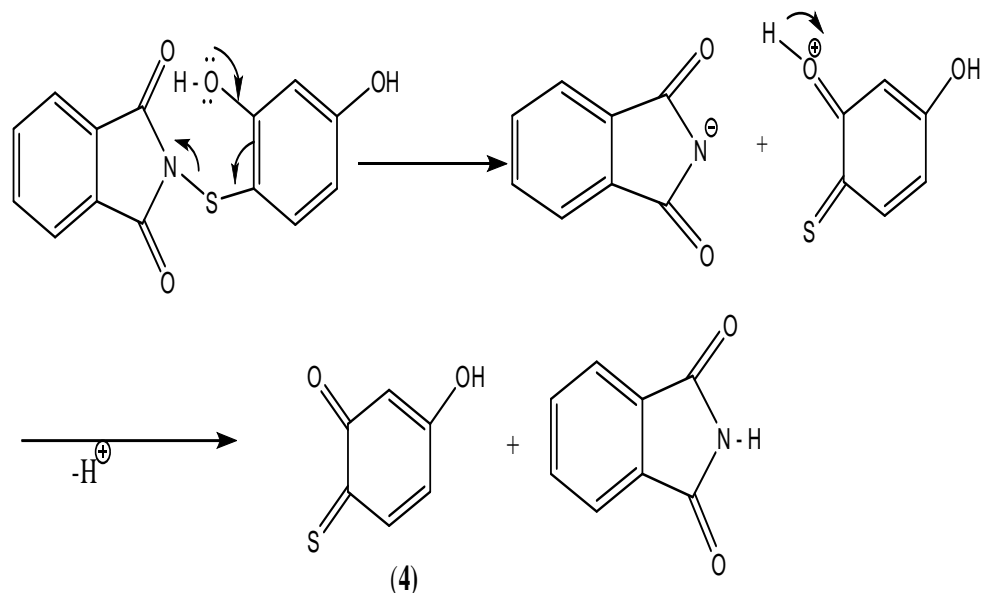


Figure:4 Ortho thio quinone

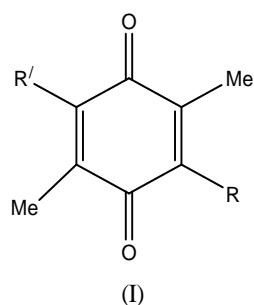
Mechanism suggested for the formation of (4) can be rationalized as -Scheme-3



Scheme-3 Mechanism developed for the formation of ortho thio quinone (4)

In a substitution reaction, (acyl methyl) pyridinium ylides react with benzo or naphthaquinones and afford the corresponding acyl methylated quinones. Reaction of trimethyl benzoquinone with phenylacyl-pyridinium iodide in methanol or MeCN containing Et₃N for 24 hrs

resulted 40-60% acyl quinones I(R=CH₂COPh,R'=Me). Reaction of I (R=R'=H) with 1,3-indandione in EtOH containing pyridine at room temperature yields 5 (R=H, R'=Q)[13].



I, (R'=Q)

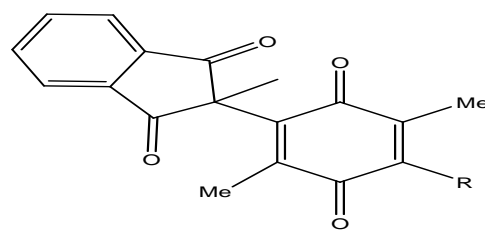
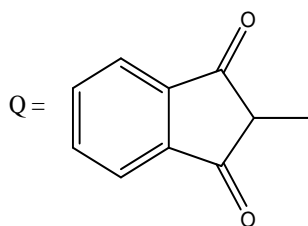


Figure:5,R'=Q

Condensation reaction of p-RC₆H₄CHO (R=MeO,H,NO₂) with 1,3-indandione,barbituric acid and dimedone in DMF results the corresponding 2-arylidene-1,3-indandiones,5-arylidene barbituric acids and 9-aryl-tetramethyl-octahydro xanthenes dione(6)

respectively in good yields in absence of catalyst but the product yield increases in presence of Polymeric amino propane sulphonic acids based on styrene-divinyl benzene copolymer.

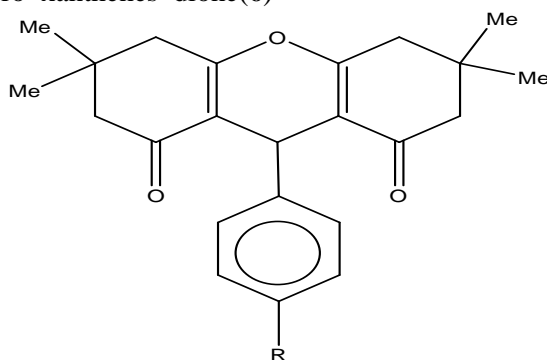
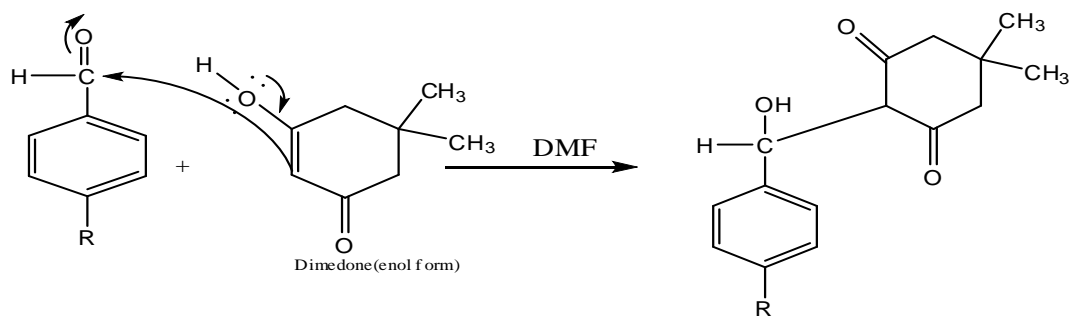


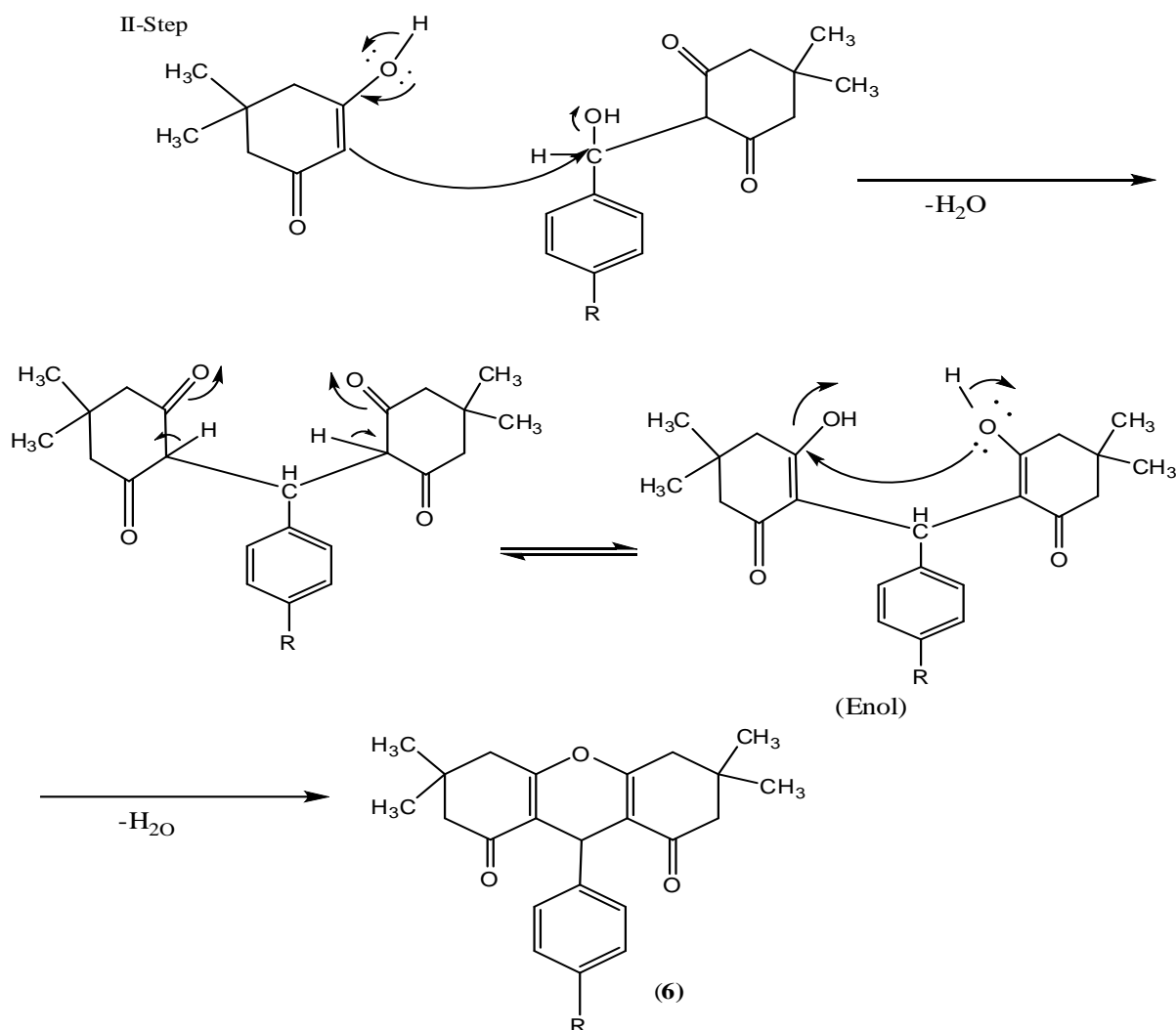
Figure:6 9-aryl-tetramethyl-octahydro xanthenes dione

Plausible mechanism developed for the formation of (6) can be depicted as –Scheme-4

I-Step



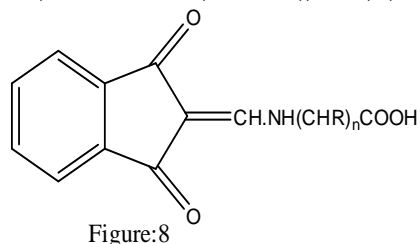
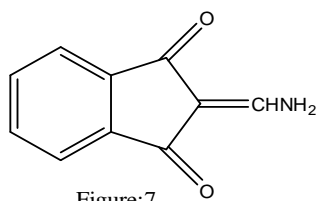
II-Step



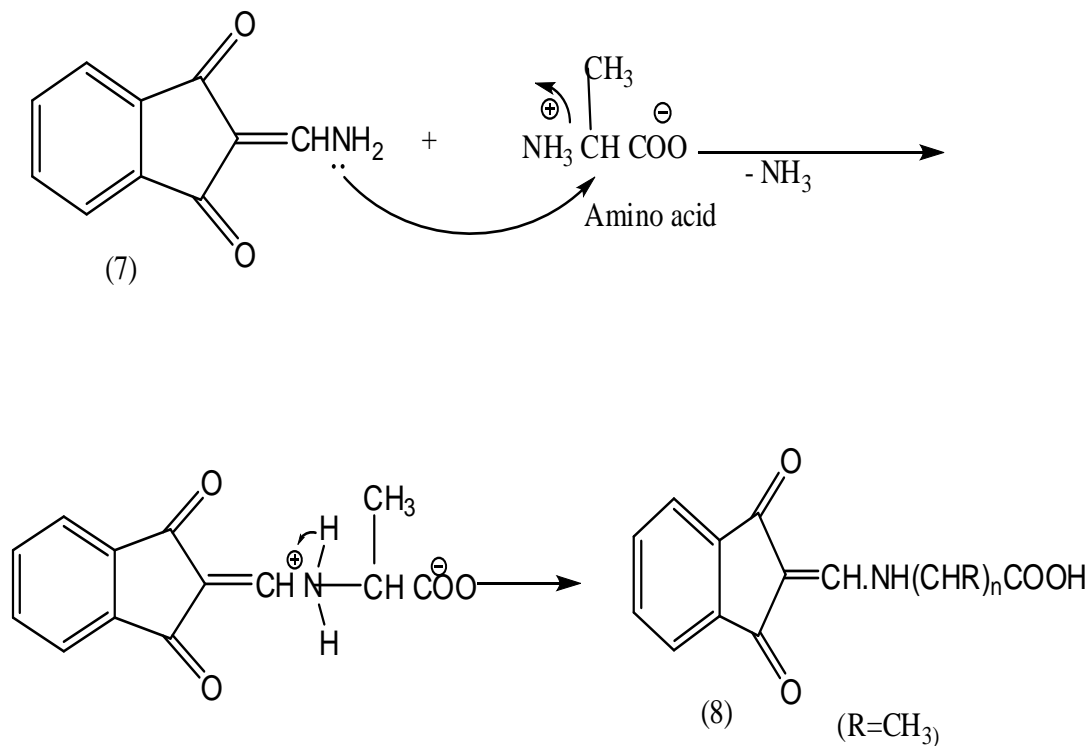
Scheme-4 Proposed mechanism for the formation of (6)

Reaction of 1,3-indandione with $\text{HC}(\text{OEt})_3$ and NH_3 afforded (7) in high yields which then reacts with amino

acids to give (8) ($n=1, R=H, \text{Me}, \text{CH}_2\text{CH}_2\text{SMe}, \text{Me}_2\text{CH}, n=2, 3, R=H$).



Possible mechanism developed for the formation of (8) can be discussed as below **Scheme-5**



Scheme-5 Suggested mechanism developed for the formation of (8)

Acetyl and cinnamoyl indandiones **9** (R=Me,CH = CHPr) react with aminozoles such as 3-amino-1,2,4-triazole and 2-aminobenzimidazole to give indenoazolo-

pyrimidines (**10**) and (1,3-dioxo-indan-2-yl)-azolopyrimidines (**11**) respectively[14]

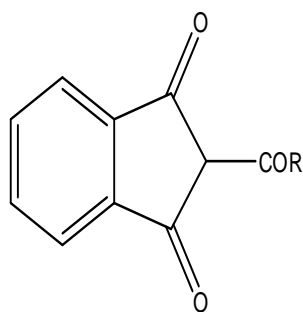


Figure:9 Acetyl and cinnamoyl indandiones

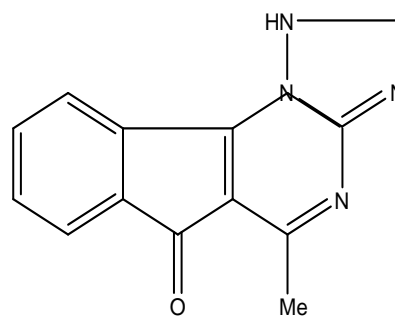


Figure:10 Indenoazolo-pyrimidines

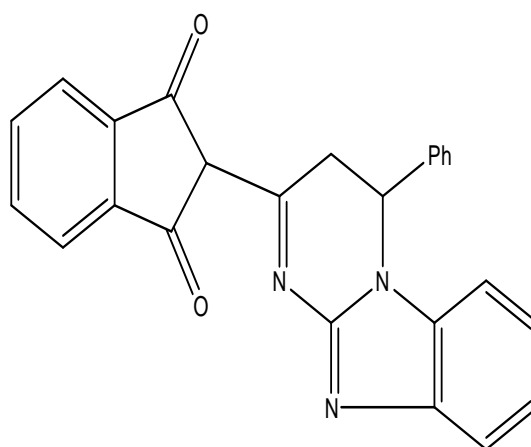
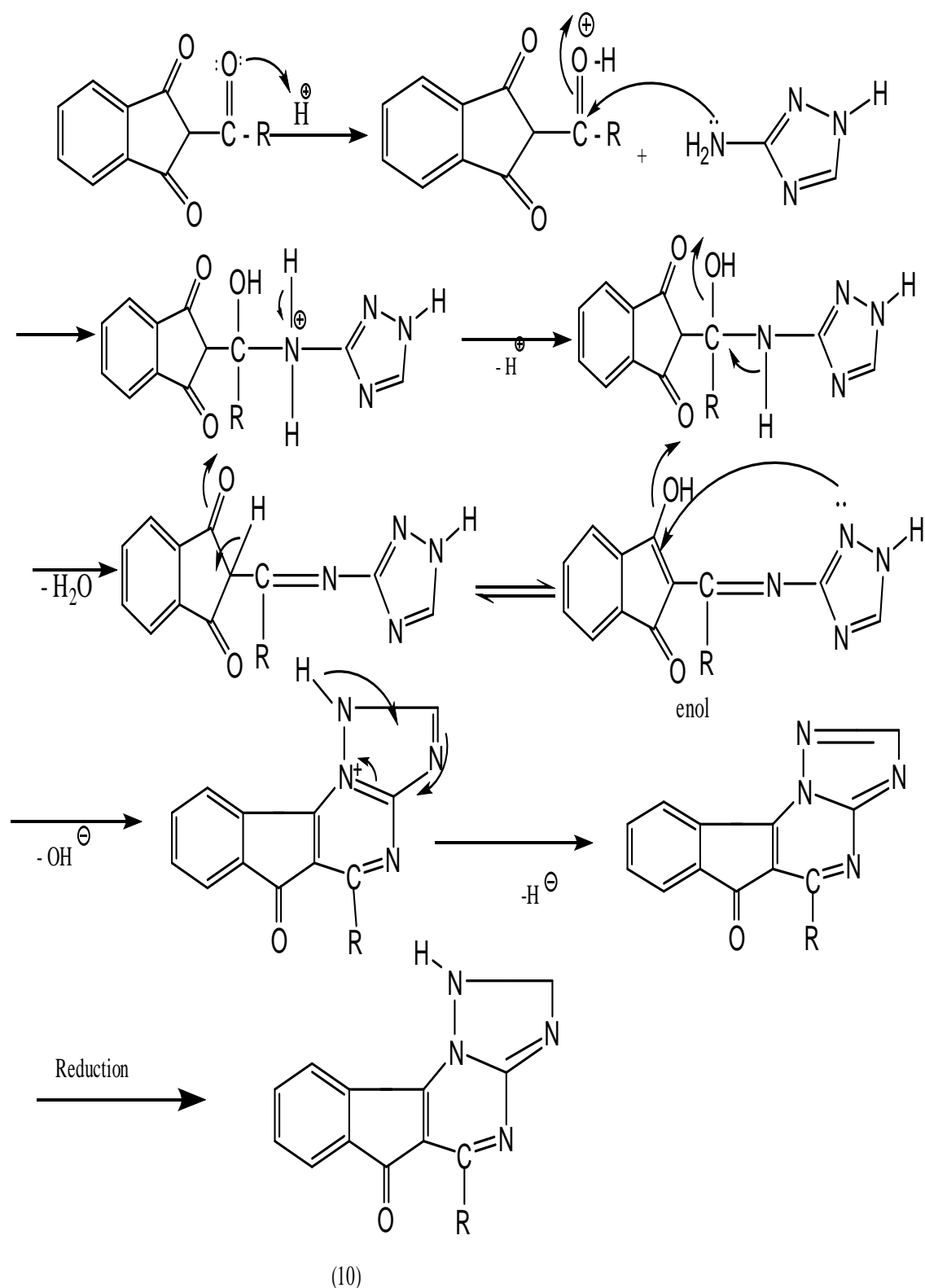


Figure 11 (1,3-dioxo-indan-2-yl)-azolopyrimidines

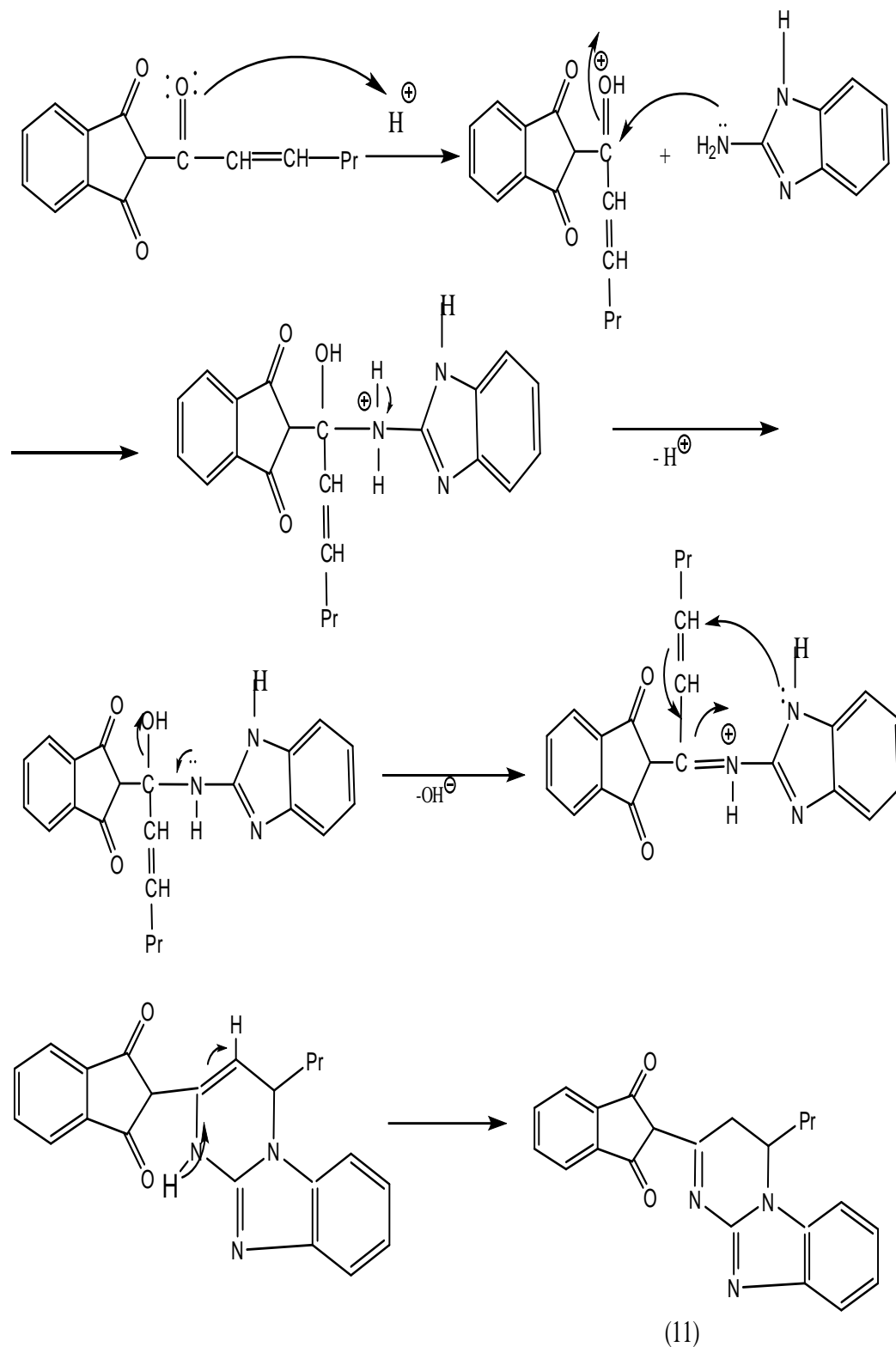
Acid catalyzed mechanism developed for the formation of **(10)** can be rationalized as given below. **Scheme-6**



Scheme-6 Mechanism developed for the formation of **(10)**

Plausible mechanism proposed for the formation of **(11)** can be depicted as below. The mechanism is

believed to proceed in presence of acid catalyst **Scheme-7**



Scheme-7 Proposed mechanism for the formation of (11)

3. Conclusion

1,3-indandione has been used as a model substrate in a wide range of organic compounds. 2-(benzyl,Pr.substituted)-1,3-indandiones (1) synthesized from 2-phenyl-substituted-1,3-indandione with beta-chloro vinyl ketones have been evaluated for different potential bioactive properties. Ortho thio quinones (4), a class of versatile intermediate dienes

have been utilized to prepare a series of heterocycles of immense pharmacological importance

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