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Mechanistic investigation of some pharmacologically active beta-diketo compounds and related nitrogen heterocycles, A theoretical approach

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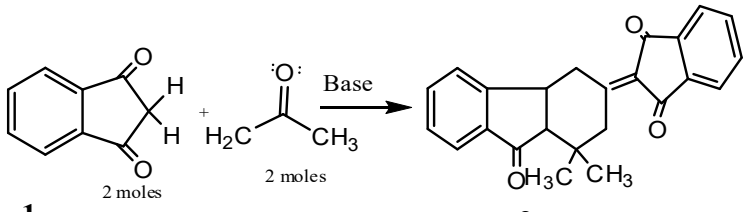
ABSTRACT

Beta-diketo compounds and related N-heterocycles have played a significant role in synthetic organic chemistry. A multistep mechanism for a catalyze base reaction of 1,3-indandione **1** with acetone has been developed to afford a complex molecule, 3-(1,3-Dioxo-2-indanylidene)-1,1-dimethyl-1,2,3,4,4d, 9a-hexahydrofluorene **2**. Pharmacologically active compounds **3**, with anticoagulant and antispasmodic properties, have been synthesized through the reaction of 2-substituted 1,3-indandione with β-chloro-vinyl ketones. Interaction of phthalimide **4** with benzyl chloride in DMF in presence of K_2CO_3-Al_2O_3 leads to the formation of N-benzyl phthalimide **11**.N-substituted products of type **15** and **16** have been obtained when 6-alkyl or aryl -4(aryl methyl) pyridazine-3(2H)-ones **14** interacted with Bromo-ethyl acetate and acetic-anhydride respectively. However, 3-chloro substituted pyridazines **17** afforded 3-mercaptopyridazine derivatives **18** when interacted with thiourea. In this paper, we suggest multistep mechanisms for a series of compounds and all the proposed mechanisms are unknown.

GRAPHICAL ABSTRACT



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INTRODUCTION

1,3-indandione, an important member of the class of β-diketo compounds, has been found to yield a series of compounds of both pharmacological and chemical importance. [1-2] Its interaction with cyclo-pentanone and cyclohexanone furnishes the corresponding 2-cycloalkylidene-1,3-indandione [3], shows Michael addition reaction with β-nitro vinyl benzene to give an adduct having fungicidal property depending upon the type and location of the substituent on aryl residue [4]. In a double Michael addition reaction, 1,3-indandione has been found to interact with 1,5-diphenyl pentadiene-3-one in a (-) quinine catalyzed stereospecific reaction to give optically active trans spiran. It affords 5-Bromo furfuryl diindandionyl-methane with 5-Bromo furfural in ethanol [5]and furnishes a condensation product with indazoladione [6]. The 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.[7].7-Nitro-2pyridyl-1,3-indandione has been successfully converted to 3-chloro-7-nitro-2-pyridyl indenone which suffers nucleophilic substitution with primary aliphatic or aromatic amines to give a range of possible oral anticoagulants. In an interesting regioselective reaction, the acetylation of 2-acyl-1,3-indandione with ketene takes place exclusively at the enol of the acyl group and not at the enol of any indandione carbonyl. The 2-acyl derivatives (R/=CH_3, Ph, Et, etc.) react with primary amines preferentially at acyl-carbon to form 2-(1-imino alkyl or aryl) 1,3-indandiones. Nitrogen heterocycles or allied nitrogen-containing ring compounds have also been used as substrates in different reactions. Interaction of NH-containing nitrogen heterocycles such as 1,7-naphthyridine-4-one with DMSO at elevated temperature, yields the corresponding N-methyl thiomethyl ether,[8] whereas 4-hydroxy 1,6-naphthyridene results in a dinaphthyridinyl methane [9]. N-hydroxy methylation of phthalimide has been achieved by refluxing it with formaldehyde.[10] A tetracyclic compound of immense pharmacological and mechanistic interest has also been synthesized from the reaction of 2-arylidene 1,3-dione with aminozoles. This is purely a theoretical paper citing references of significant chemical and pharmacological importance of varied 1,3-di-keto compounds and allied N-heterocycles. Therefore, I thought it better to highlight the pharmacological activity of some known compounds and simultaneously proposed certain new plausible multistep mechanisms for different compounds which were not discussed or proposed earlier as revealed by the exhaustive literature survey on the subject.

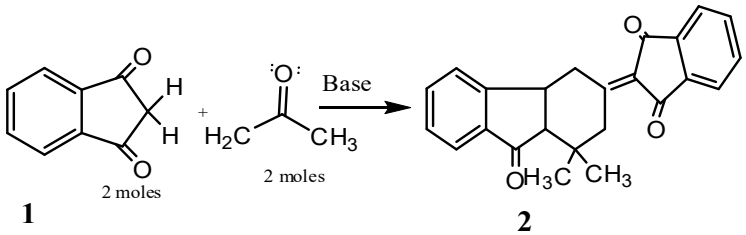


Fig. 1 1,3-indandione (2 moles) affords a complex molecule 3-(1,3-Dioxo-2-indanylidene)-1,1-dimethyl-1,2,3,4,4d,9a-hexahydrofluorene **2,** when allowed to react with acetone (2 moles).

Results and discussions

1,3-indandione **1**, a di-keto compound, containing an active methylene group, has been used as a model substrate in a wide range of reactions yielding a variety of C-2 substituted products. These products have been further transformed to different adducts of both chemical and mechanistic interest. In an interesting base catalyzed condensation reaction, 1,3-indandione (2 moles) affords a complex molecule 3-(1,3-Dioxo-2-indanylidene)-1,1-dimethyl-1,2,3,4,4d,9a-hexahydrofluorene **2,** when allowed to react with acetone (2 moles). [11,11a]

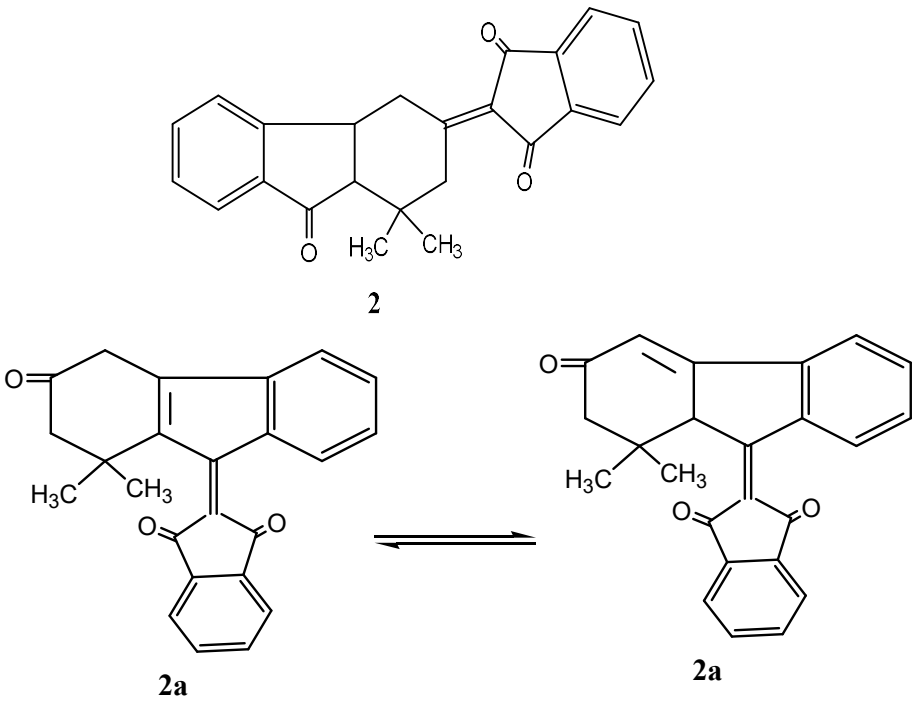


Figure 2. 3-(1,3-Dioxo-2-indanylidene)-1,1-dimethyl-1,2,3,4,4d,9a-hexahydrofluorene, **2a**: Earlier proposed structure for **2**

A mixture of 140 ml of acetone,15 g of 1,3-indandione, and 7g of piperidene was heated under reflux on a water bath for 1 h and then allowed to stand at room temperature for 5 h. The dark blue solution was added in small portions to 1.5 l of well-stirred 10% aqueous acetic acid. The brownish-yellow precipitate was filtered, washed with water, and then several times with alcohol. After the alcohol treatment, the solid was washed with 10% Na_2CO_3 solution and then with 10% aqueous acetic acid solution. The yellow mass was dried and crystallized from glacial acetic acid yielding 9.7g of product**,** m.p 198-200^{0}C.

The author has minutely gone through the earlier published work of the above-placed structure and observed that this structure is a modification of the already postulated and published structures in an earlier paper and it is clear that no attempt has been made to date to develop any type of mechanism to confirm the structure. [11] Therefore a unique multistep-step mechanism proposed the first time for the formation of 2 can be depicted as below. In this reaction, piperidene has been used as the base.

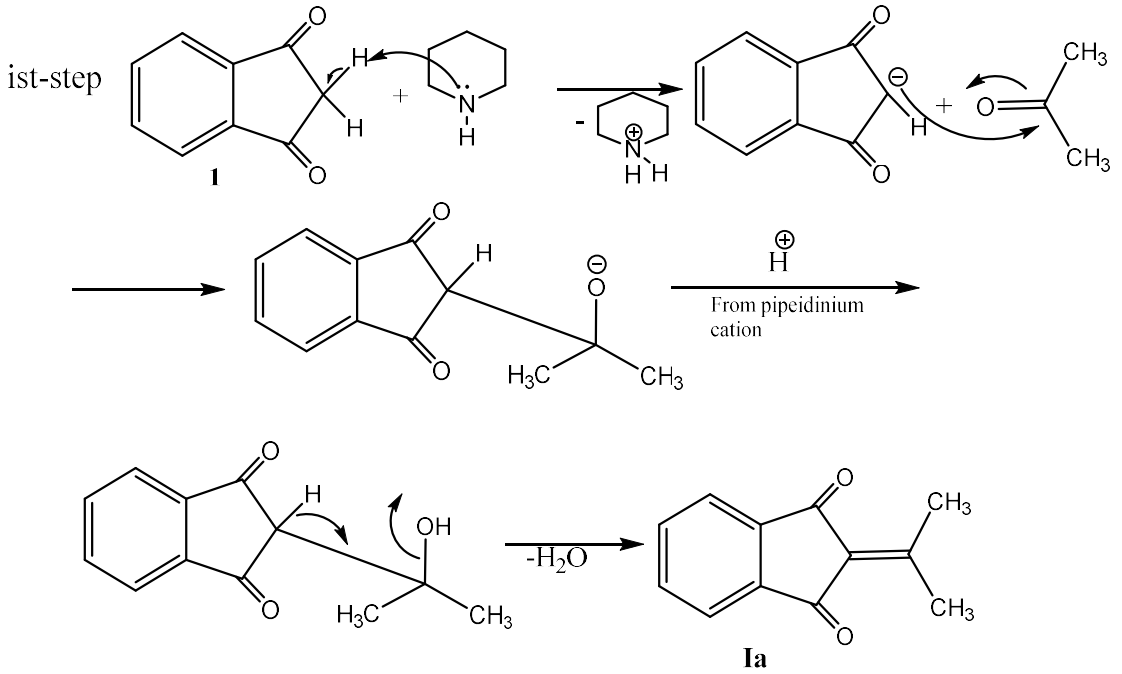


Fig. 3.1,3-indandione, 2-dimethylmethylene-1,3-indandione, **2nd-step**:- Interaction of **Ia** with the second mole of acetone in presence of a base.

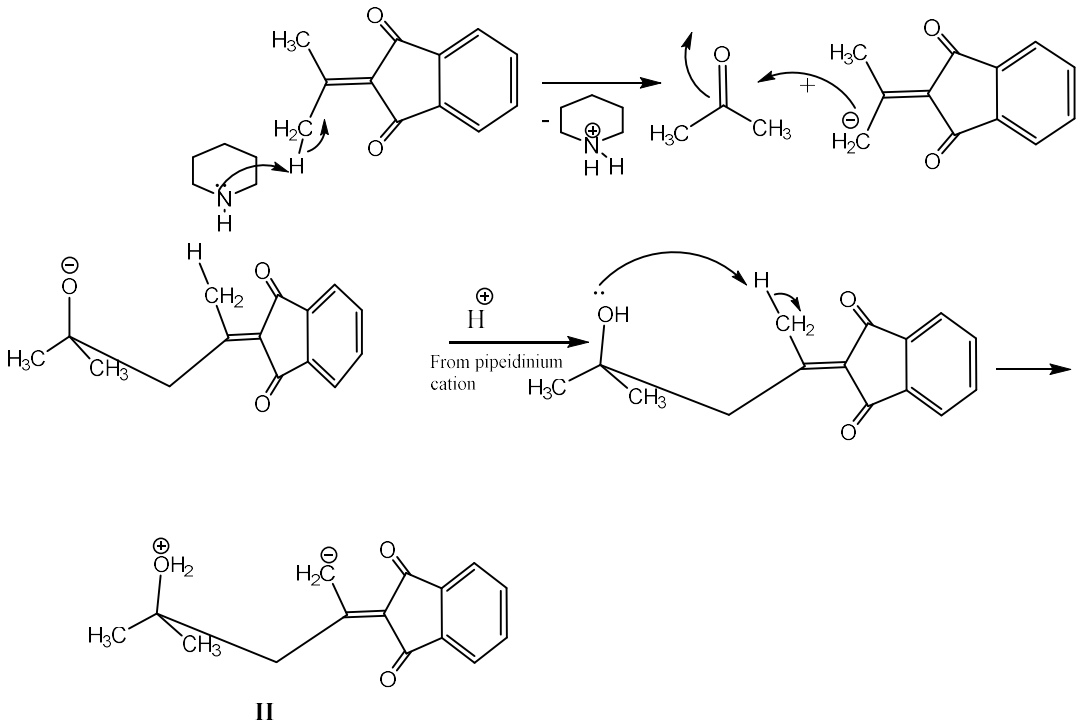


Fig 4, 3rd-step: Interaction of II with base-catalyzed 2nd molecule of 1,3-indandione(enol form) to form the adduct

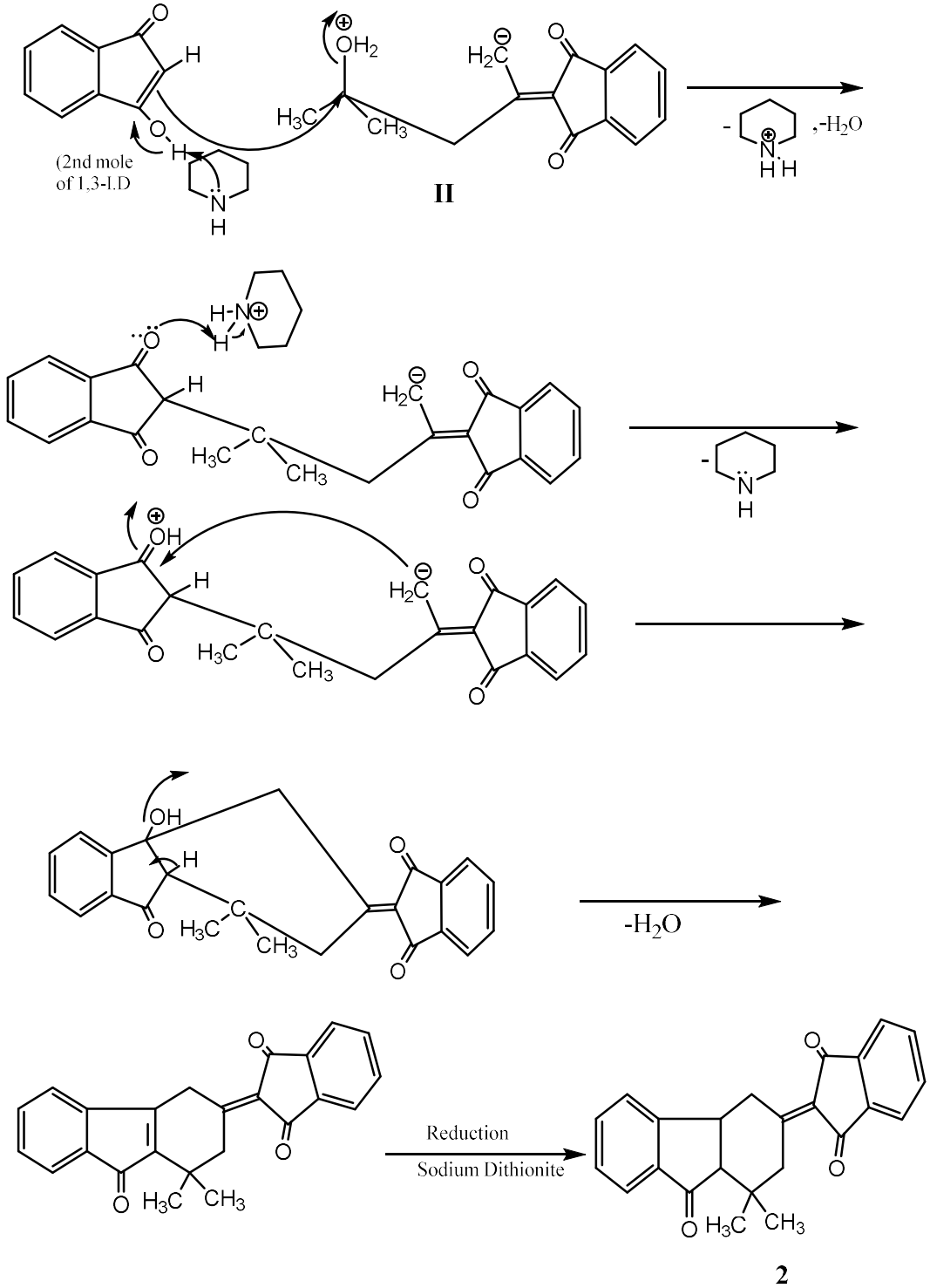
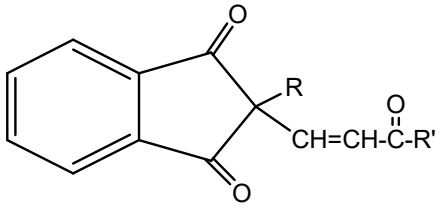


Fig. 5 M*ultistep mechanism developed for the formation of 3-(1,3-Dioxo-2-indanylidene)-1,1-dimethyl-1,2,3,4,4d,9a-hexahydrofluorene(* 2).

A range of pharmacologically active compounds **3**, with anticoagulant and antispasmodic properties have been synthesized through the reaction of 2-substituted 1,3-indandione with β-chloro-vinyl ketones [12].

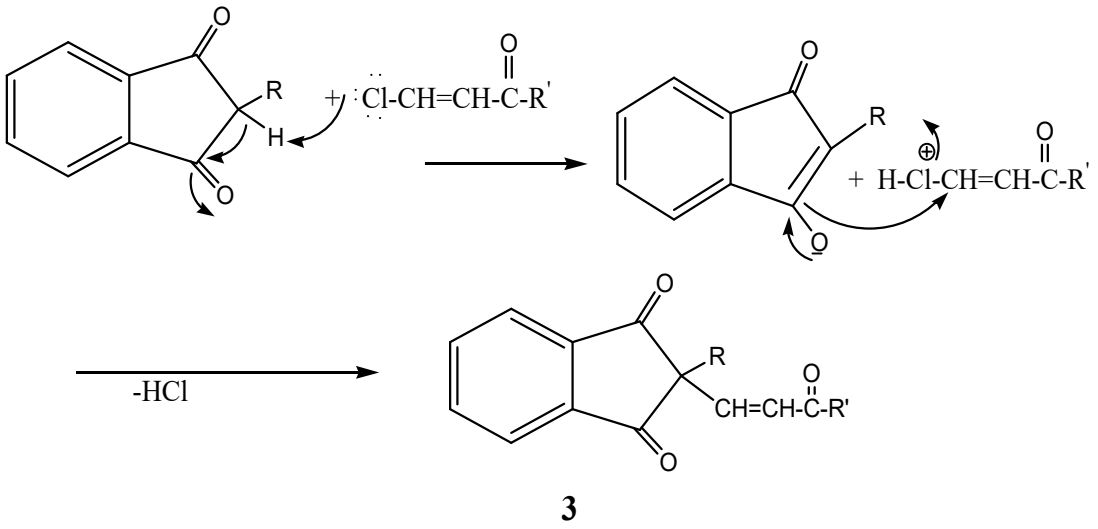


3 R=Ph,Me etc.

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

Fig. 6. 2-Substituted derivative of 1,3-indandione 1

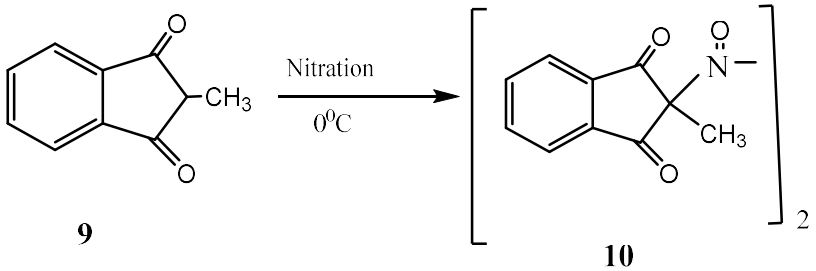
The plausible mechanism developed for the formation of (Fig. 6) can be rationalized as Fig 7.



3

Fig. 7 *The suggested mechanism for the formation of* **3**

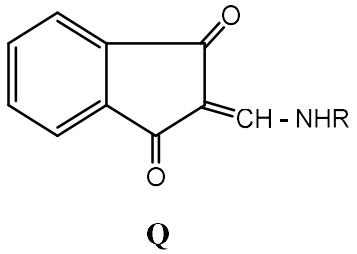
In an interesting reaction, nitration of 2-methyl-1,3-indandione **9** with fuming nitric acid in acetic acid has been carried out below 0^0C to afford 2-nitroso-2-methyl-1,3-indandione dimer **10** as the final product [13].



9 **10**

Fig. 8. 2-methyl 1,3-indandione converts to2-nitroso-2-methyl-1,3-indandione dimer **10**

In an identical mechanistically interesting reaction, 2-formyl derivative of 1,3-indandione **1** has been found to interact with primary amines such as derivatives of aniline [14] to give enamines of the type (Fig 9).



Q

Fig. 9. Enamine of 2-formyl derivative of 1,3-indandione **1**

The addition of amine to the formyl group of 2-formyl 1,3-indandione derivative is believed to be an acid-catalyzed reaction and therefore the mechanism proposed for the formation of(Fig. 9) follows as Fig 10.

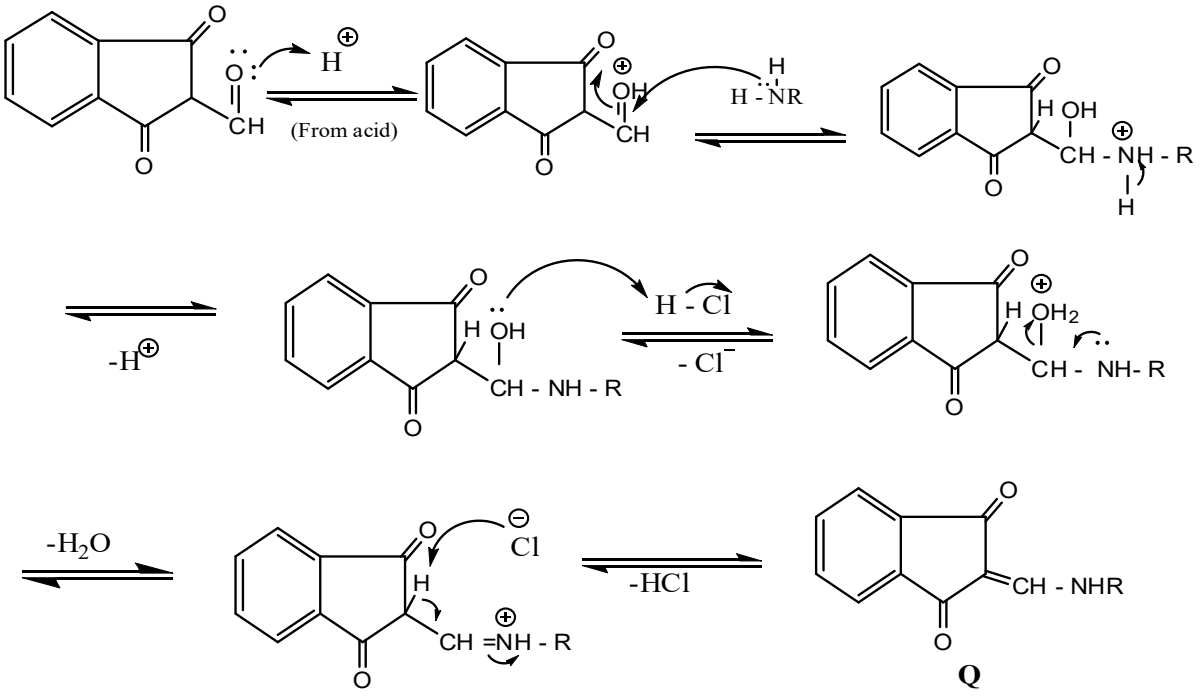
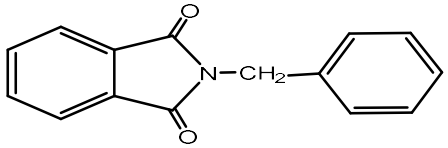


Fig 10. *The mechanism for the formation of* ***Q***

1H –isoindole-1,3-(2H) dione and allied nitrogen heterocycles have played a significant role in synthetic organic chemistry. Phthalimides **4** and their related 3-alkyl and 3-aryl methylene-2,3-dihydro-1H-isoindoline-1-ones have been found to possess a wide range of therapeutic applications [15]. N-substituted derivatives of phthalimide have frequently been synthesized

[16-17]. Interaction of phthalimide **4** with benzyl chloride in DMF in presence of K_2CO_3-Al_2O_3 leads to the formation of mechanistically interesting N-benzyl phthalimide (Fig 11) [18].



11

Fig. 11. N-benzyl phthalimide

The probable mechanism suggested for the formation of (Fig. **11)** can be discussed as **Fig. 12**

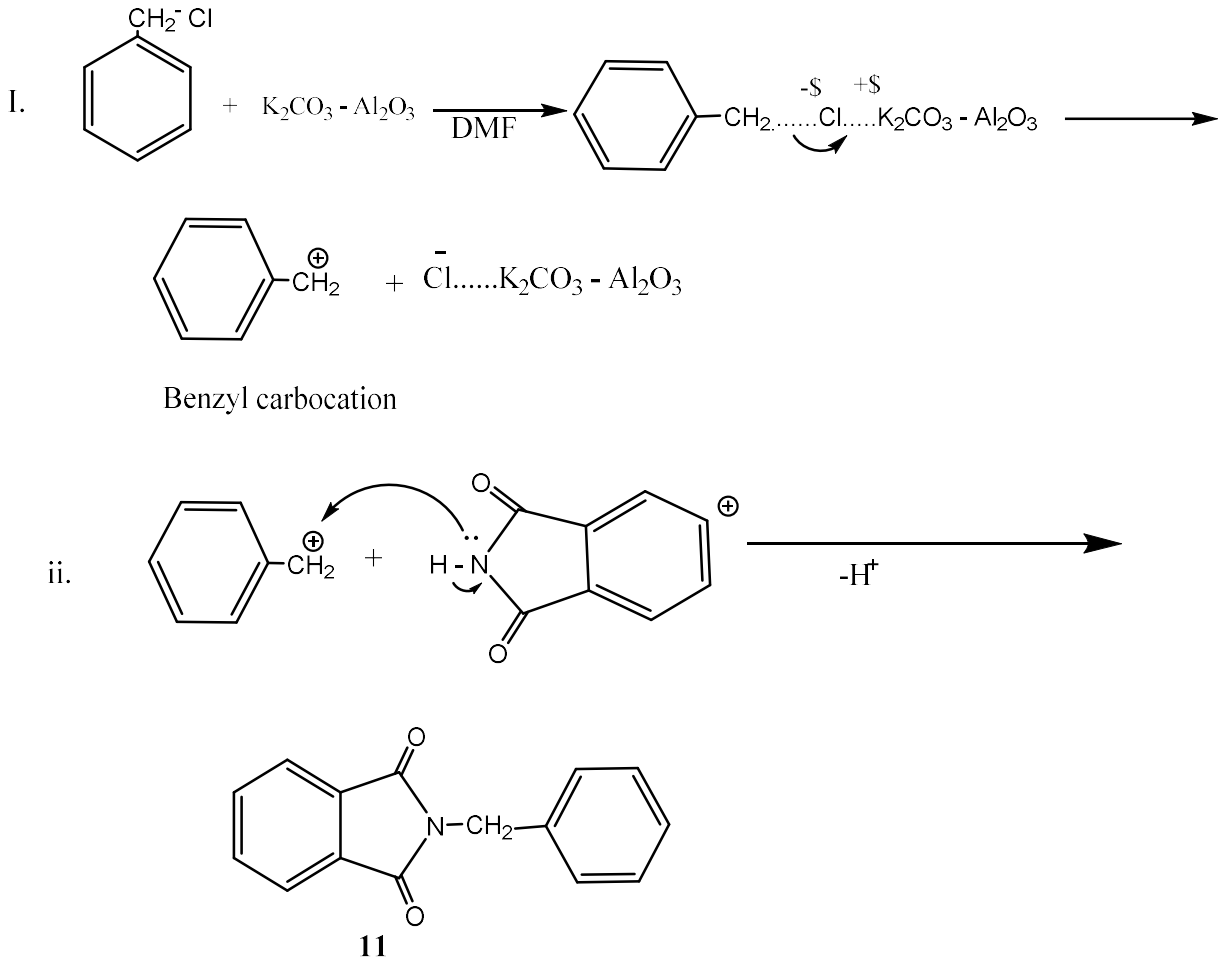


Fig 12. *The mechanism proposed for the formation of* (**11)** *from benzyl chloride*

In an important substitution reaction 1H – isoindole-1,3-(2H) dione **4** replaces chloride from chloroacetonitrile to yield N-cyanomethyl phthalimide **12** [19].

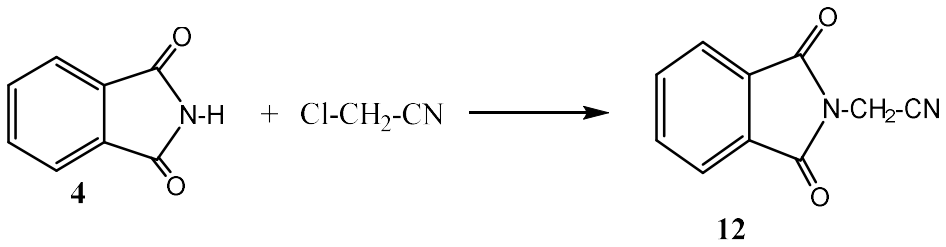


Fig 13. Phthalimide transforms to N-Cyanomethyl phthalimide (**12)**

Mechanistically the formation of (Figure 13**)** can be rationalized in the Fig. 14.

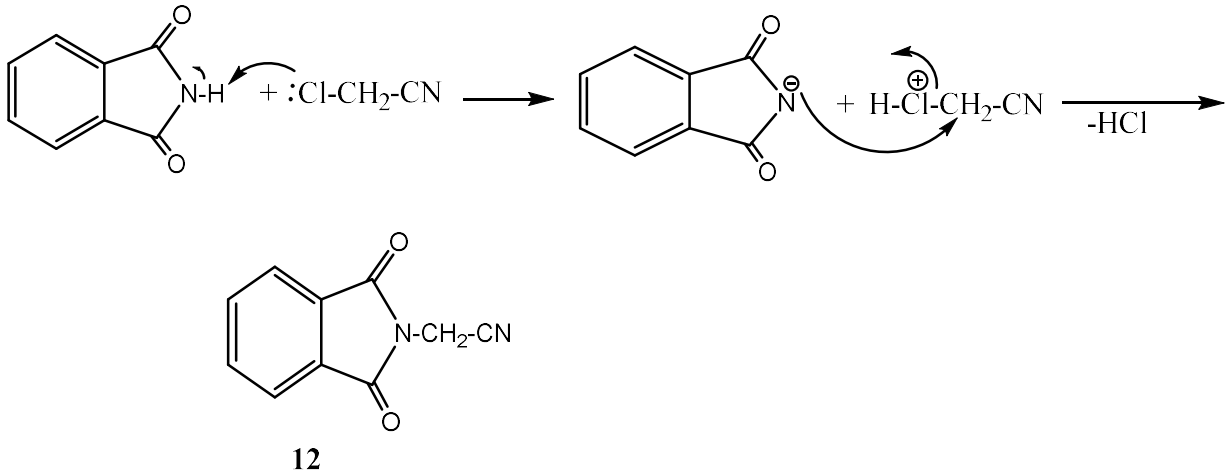
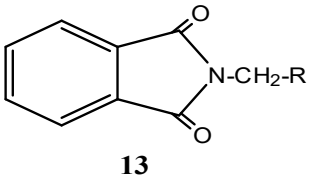


Fig 14. *The suggested mechanism for the formation of N-Cyanomethyl phthalimide*

Kinetic assessment of N-hydroxymethyl derivatives of phthalimide (Fig. 13) has been studied as possible prodrugs[20].



(R=OH)

Fig. 15. N-hydroxymethyl derivative of phthalimide

N-substituted products (Fig.15 and 16) of chemical and mechanistic interest have been synthesized by the interaction of 6-alkyl or aryl-4(aryl methyl) pyridazines-3 (2H)-ones with Bromo-ethyl acetate and acetic anhydride respectively [21-22].

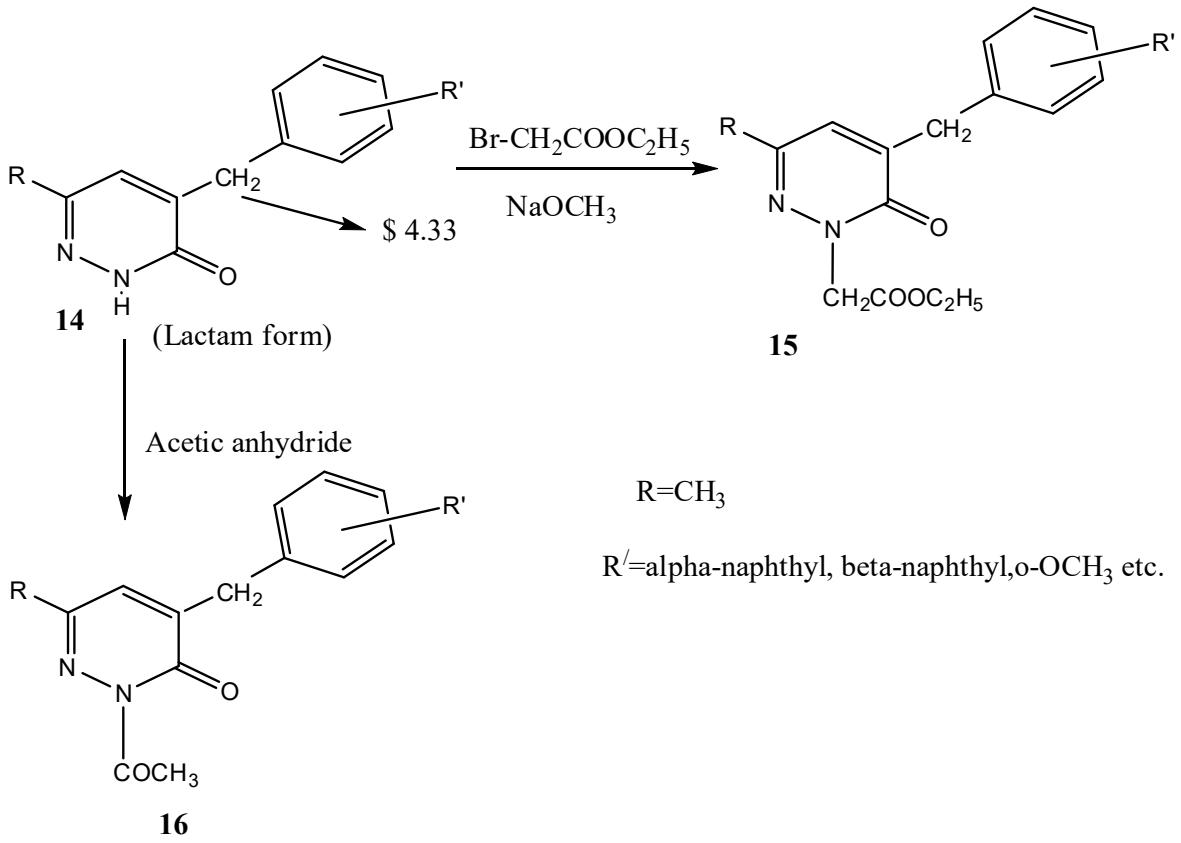


Fig. 16. 6-alkyl or aryl-4(aryl methyl) pyridazines-3 (2H)-ones convert to its N-substituted products **15** and **16.**

While going through the contents of the earlier published paper [21], it has been observed that the mechanism is not known. So, the formation of products 15 and 16 can be confirmed by the following proposed mechanisms discussed as :

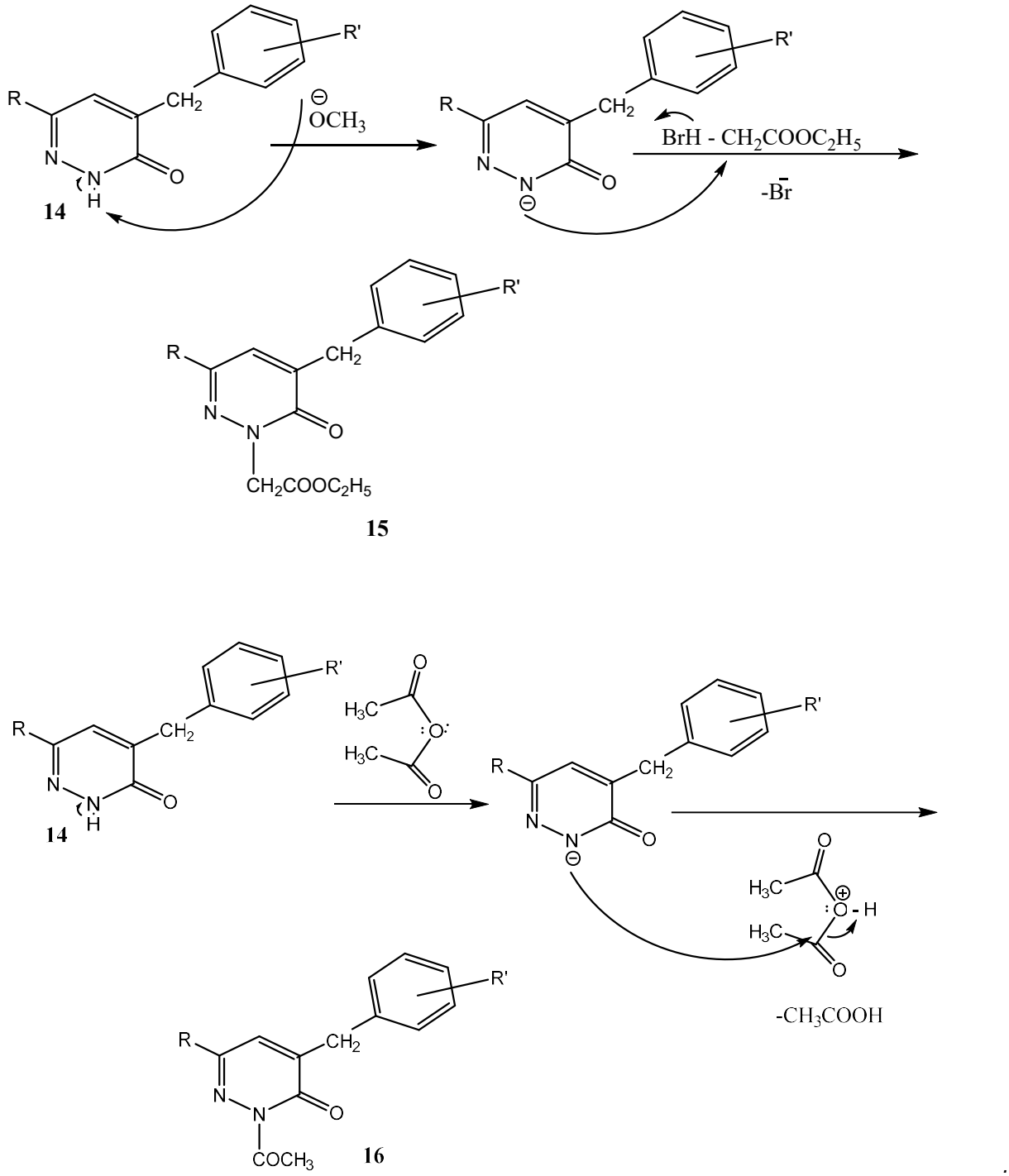


Fig. 17*. Proposed mechanism for the formation of product 15 and 16.*

In a similar mechanistically interesting reaction, 3-mercaptopyridazine derivatives 18 have been obtained by the interaction of 3-chloro substituted pyridazines 17 with thiourea.

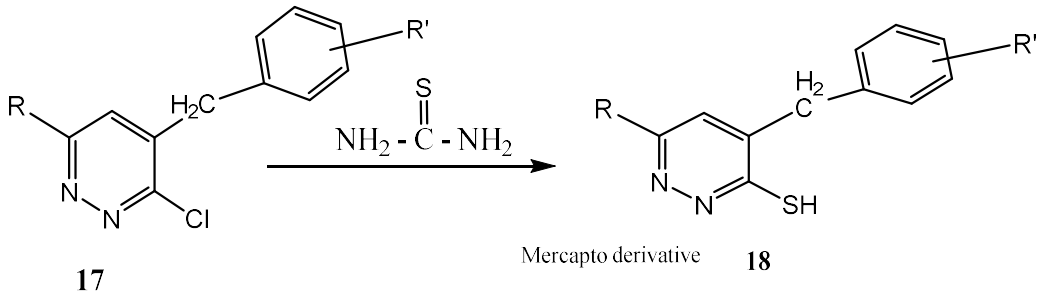


Fig. 18. 3-Chloro substituted pyridazine converts to mercapto derivative (**18)**

Since the mechanism was not known earlier, therefore, the plausible mechanism proposed for the formation of **18** can be depicted as:

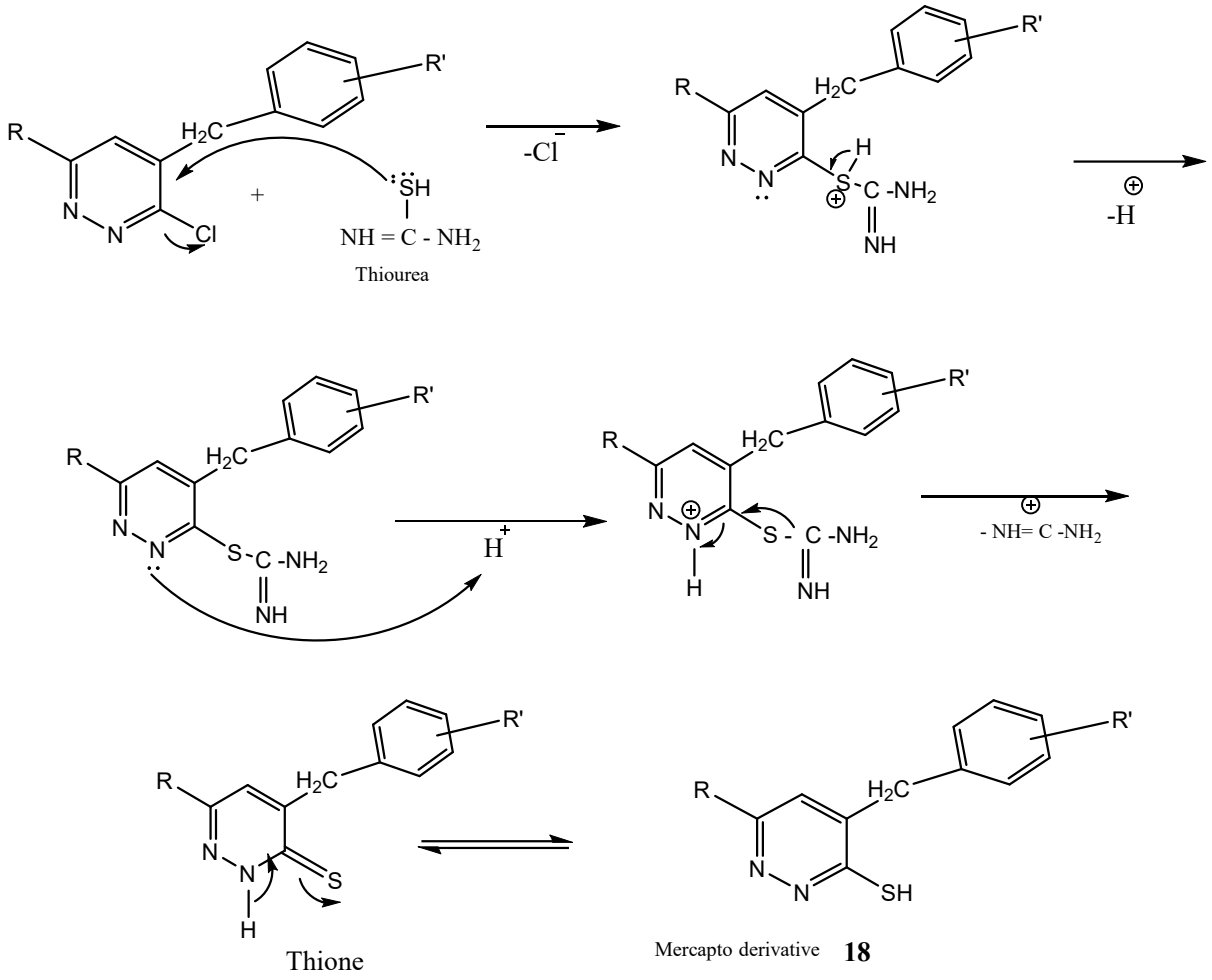


Fig 19. *A plausible mechanism for the formation of mercapto derivative* (***18)***

Mercapto derivative (Fig. 18) upon further treatment with dimethyl sulfate, under basic conditions, affords 3-thiomethyl-pyridazine adduct (Fig. 19) of both mechanistic and chemical interest. However, when mercapto derivative (Fig. 18) is treated with acrylonitrile.it results in 3-acrylonitrile pyridazine adduct (Fig. 20).

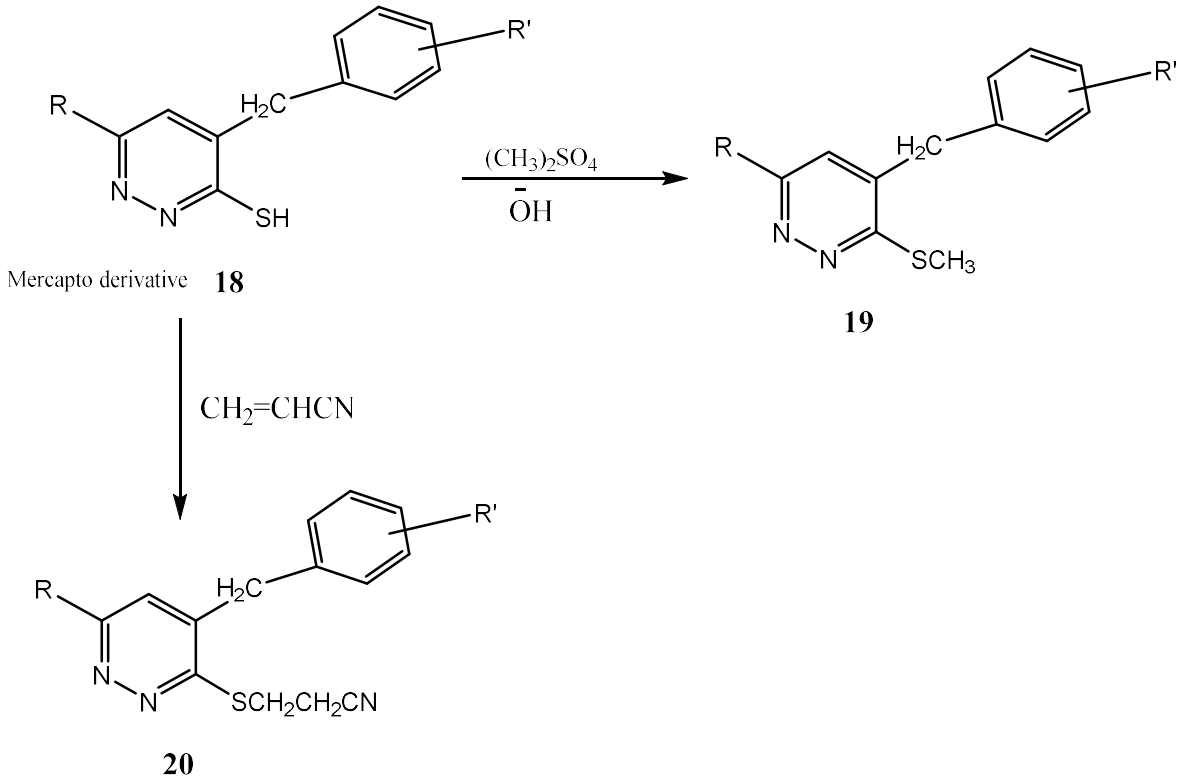
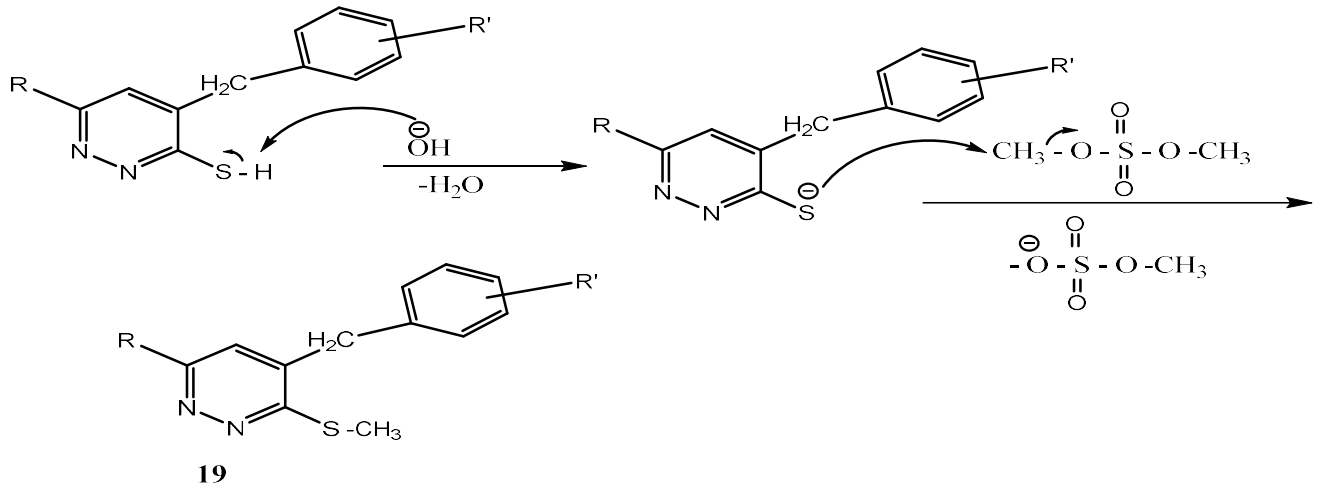


Fig. 20. Mercapto derivative of pyridazine converts to 3-thiomethyl-pyridazine adduct (Fig. 19) and 3-acrylonitrile pyridazine adduct 20.

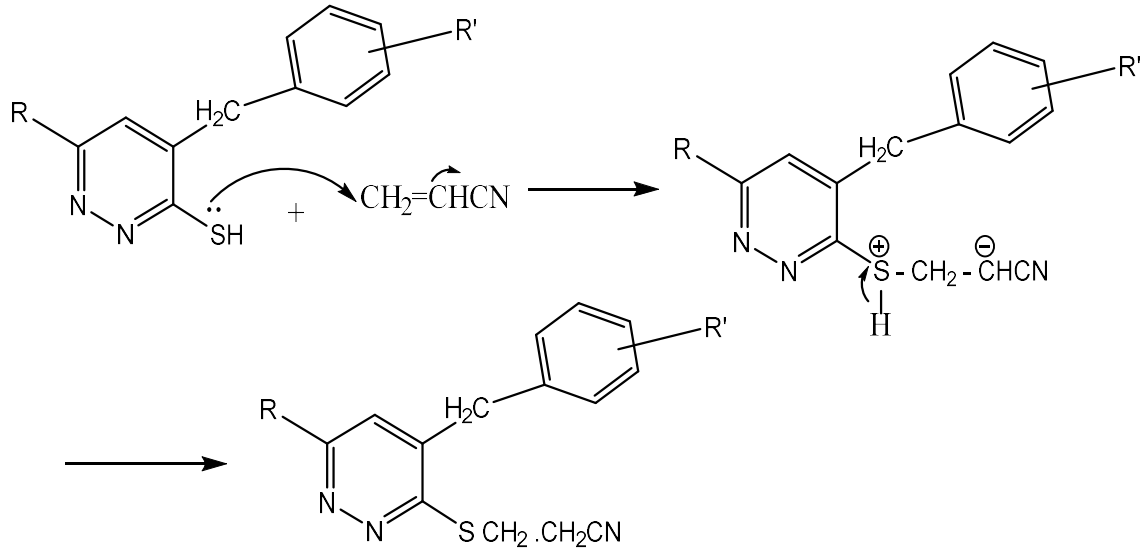
The structure (Fig. 19) has been confirmed by developing the following plausible mechanism Fig. 20



19

Fig. 21 Proposed *mechanism for the formation of* (**19)**

Again, the mechanism for the compound (Fig. 20) has not been discussed earlier, therefore, the possible mechanism suggested for its formation can be rationalized as below-Fig. 22



20

Fig. 22 *The mechanism developed for the formation of* ***20***

CONCLUSION

β- diketo compounds and their derivatives have been a subject of great research. 1,3-indandione, an important member of the class of 1,3-diketo compounds, has found marked applications in synthetic organic chemistry and has proved a model substrate for the synthesis of a wide range of compounds. Its 2-substituted derivatives have been and possibly can be further transformed to a variety of products of both pharmacological and mechanistic interest. Nitrogen heterocycles and nitrogen-containing di-keto compounds have also been used as suitable substrates for convenient synthetic transformations. The products so obtained can open a new door in the field of synthetic organic chemistry, taking advantage of new techniques through different routes. Unique multistep mechanisms have been proposed for a series of compounds displayed in this article. The mechanisms suggested for varied compounds were not discussed earlier for the products of significant chemical and pharmacological importance.

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Conflict of interest

The authors declare no conflict of interest

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