SYNTHESIS OF SOME NITROGENIOUS HETEROCYCLIC COMPOUNDS

Synthesis of Some Novel pyridone, pyrazole and 4-Thiazolidinone derivatives

A thesis Submitted By

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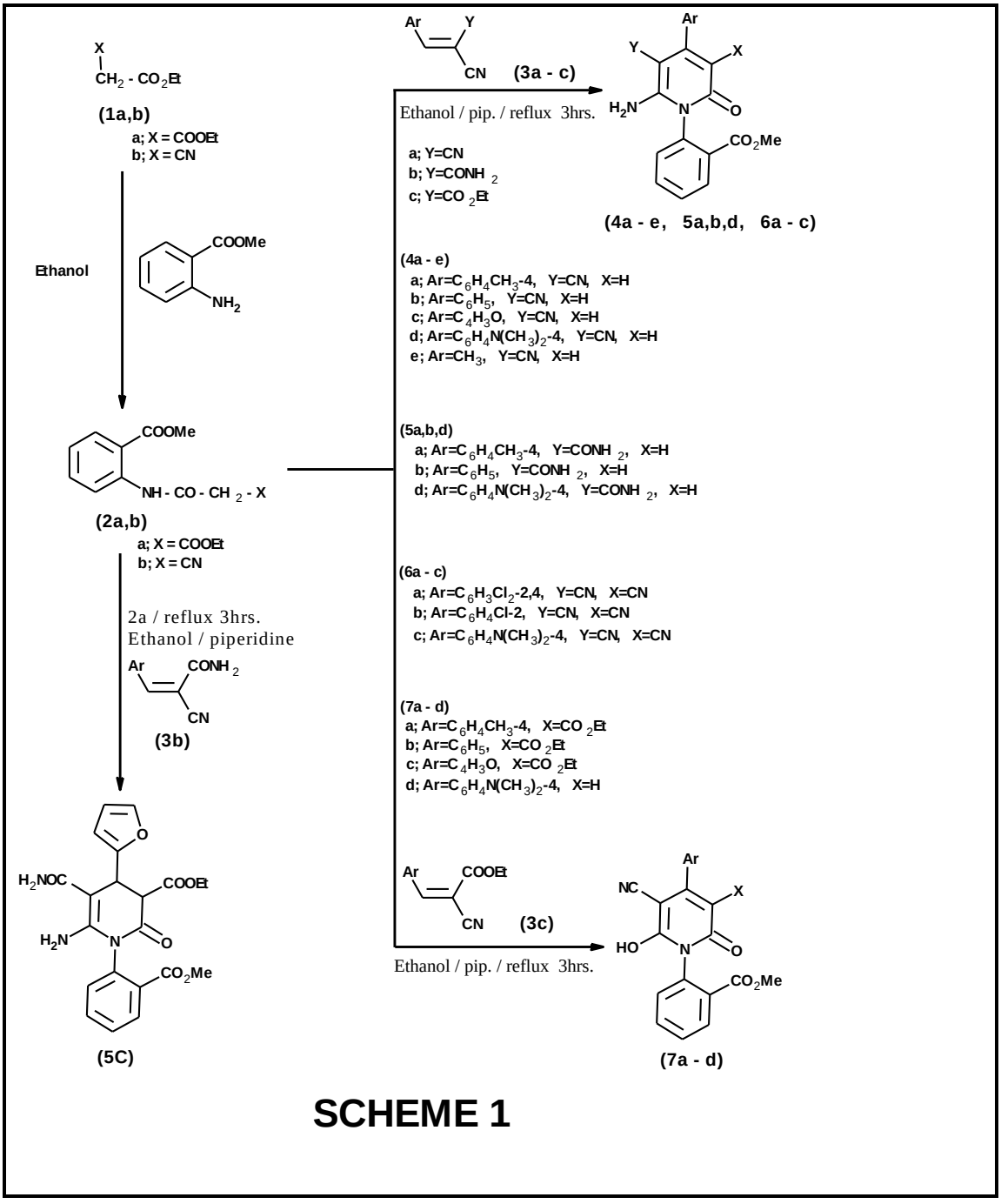
Contents

ENGLISH SUMMARY

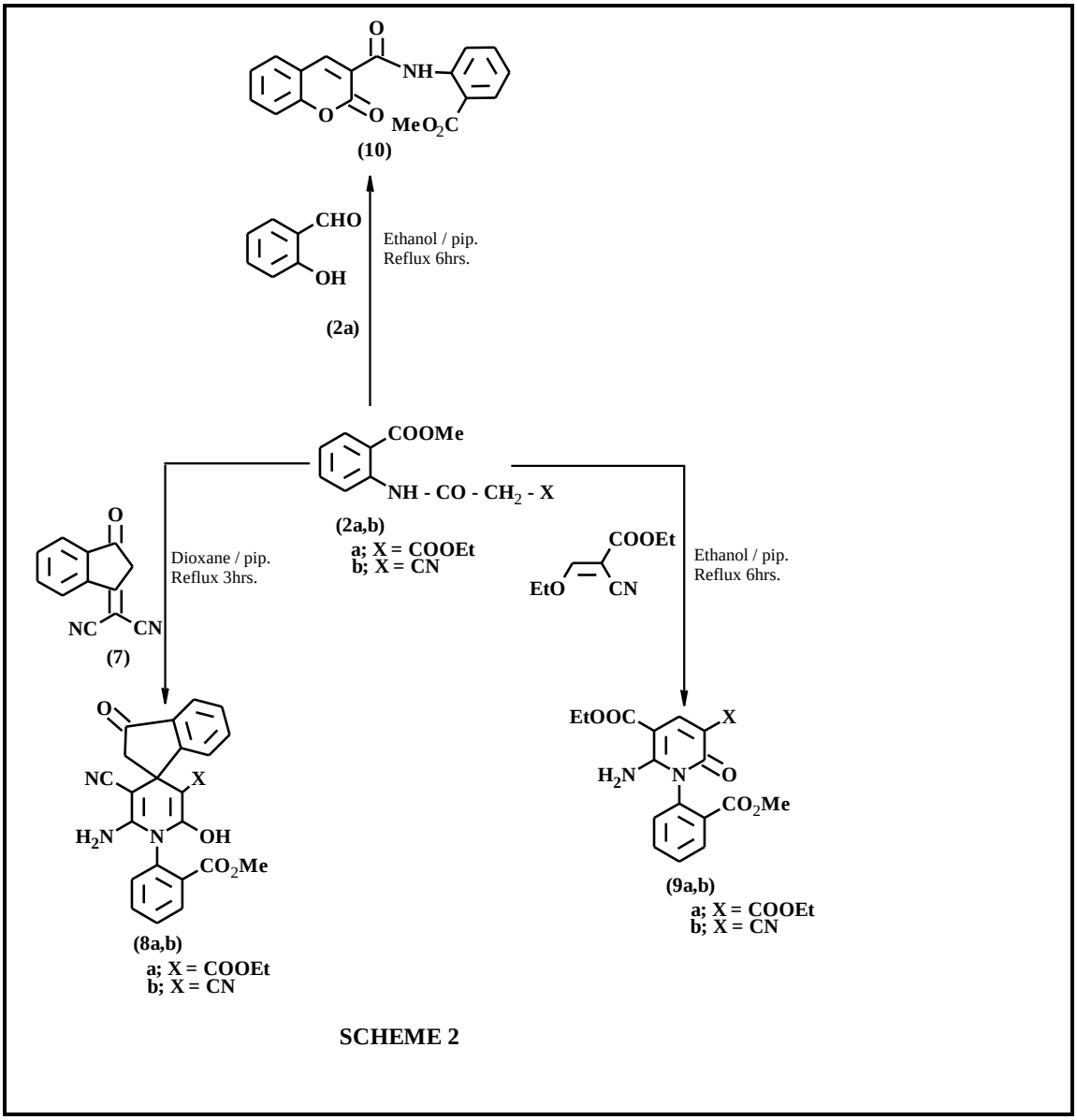
In the present investigation, the auther reported the synthesis of some novel heterocyclic compounds such as pyridone, pyrazole, quinazoline**,** 4-thiazolidinone, thiazolopyridine, thiazolonaphthyridine and pyrazolothiazolopyridine derivatives from the readily obtainable inexpensive starting materials. Thus, the active methylene derivatives diethyl malonate **(1a)** where x = CO_2Et and ethyl cyanoacetate **(1b)** where x = CN as intermediates materials were used for synthesis of 2-methoxycarbonyl acetanilide derivatives (**2a)** and **(2b)** which were used for synthesis of some novel pyridone, pyrazole and quinazoline derivatives. Also, reaction of ethyl cyanoacetate **(1b)** where x = CN as intermediate material with thioglycolic acid was used for synthesis of some novel 4-thiazolidinone, thiazolopyridine, thiazolonaphthyridine and pyrazolothiazolopyridine derivatives.

The, substituted-2-methoxycarbonyl acetanilide (**2a)** and **(2b)** were refluxed with α-substituted cinnamonitriles **(3a-c)** in absolute ethanol piperidine solution and gave the corresponding pyridones of type **(4a-e) ,(5,7)a-d** and **(6a-c)**,respectively. The formation of pyridones assumed to proceed via Michael addition of the active methylene of(**2a)** or (**2b)** at the β-carbon of α-substituted cinnamonitriles (**3a-c**) to yield the corresponding Michael adduct followed by intramolecular cyclization through nucleophilic addition of imino group to the cyano carbon then autoxidation; **Scheme 1**. The structure of pyridones was confirmed on the basis of their elemental analysis and spectral data.


(1a,b)
a; X = COOEt
b; X = CN
Ethanol
(2a,b)
a; X = COOEt
b; X = CN
2a / reflux 3hrs.
Ethanol / piperidine
(3b)
(5C)
(3a - c)
Ethanol / pip. / reflux 3hrs.
a; Y=CN
b; Y=CONH 2
c; Y=CO 2Et
(4a - e, 5a,b,d, 6a - c)
(4a - e)
a; Ar=C6H4CH3-4, Y=CN, X=H
b; Ar=C6H5, Y=CN, X=H
c; Ar=C4H3O, Y=CN, X=H
d; Ar=C6H4N(CH3)2-4, Y=CN, X=H
e; Ar=CH3, Y=CN, X=H
(5a,b,d)
a; Ar=C6H4CH3-4, Y=CONH 2, X=H
b; Ar=C6H5, Y=CONH 2, X=H
d; Ar=C6H4N(CH3)2-4, Y=CONH 2, X=H
(6a - c)
a; Ar=C6H3Cl2-2,4, Y=CN, X=CN
b; Ar=C6H4Cl-2, Y=CN, X=CN
c; Ar=C6H4N(CH3)2-4, Y=CN, X=CN
(7a - d)
a; Ar=C6H4CH3-4, X=CO 2Et
b; Ar=C6H5, X=CO 2Et
c; Ar=C4H3O, X=CO 2Et
d; Ar=C6H4N(CH3)2-4, X=H
(3c)
Ethanol / pip. / reflux 3hrs.
(7a - d)

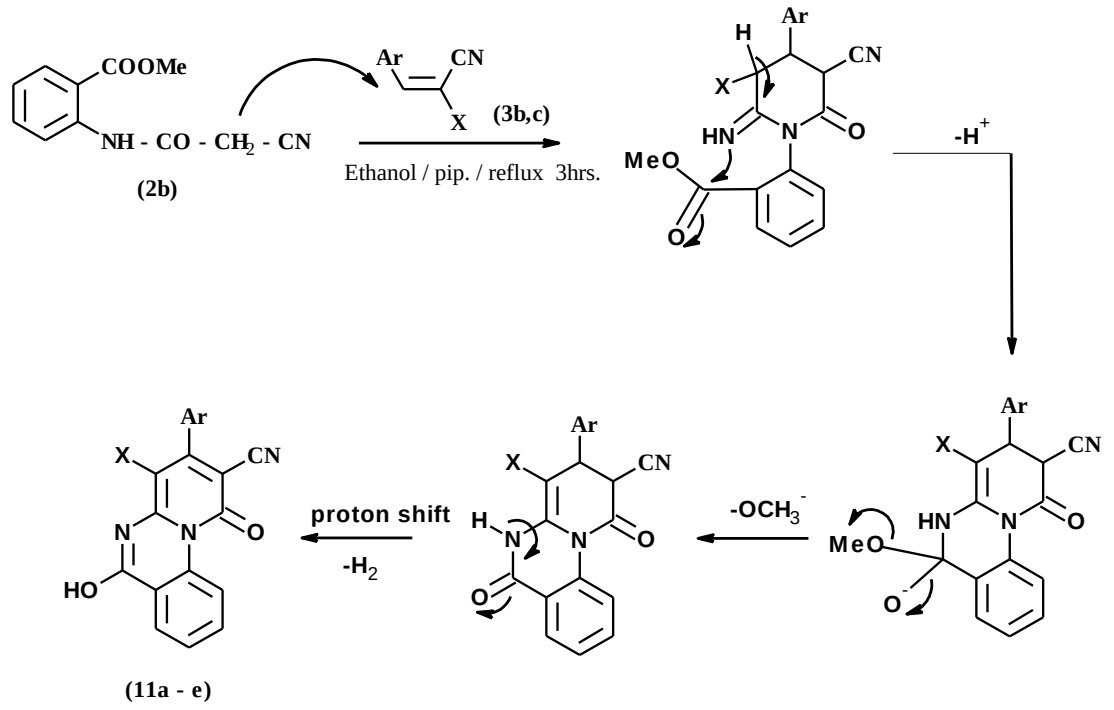
SCHEME 1

Spiro compounds represent an important class of naturally occurring molecules characterized by highly pronounced biological properties. Thus, (**2a,b)** was reacted with1,3-indandione malononitrile and gave the corresponding spiro pyridine derivatives (**8a,b)**. Also, refluxing of (**2a,b)** with 2-ethoxycarbonyl-3-ethoxyacrylonitrile afforded **(9a,b)** . The reaction of (**2a)** with salicyaldehyde in ethanol catalyzed with piperidine gave the corresponding coumarine derivative **(10)** in ethanol piperidine solution; **Scheme 2**



SCHEME 2

1,2-Dihydro-2-cyano-3-aryl-6-hydroxy-4(formamido or ethoxycarbonyl) pyrido[1,2-a]quinazoline **(11a-e)** were synthesized via cyclizatin of compound (**2b)** with α-substituted cinnamonitriles (**3b,c)** followed by elimination of methanol under reflux, the mechanistic equations for formation of (**11a-e)** can be illustrated as in **scheme 3**

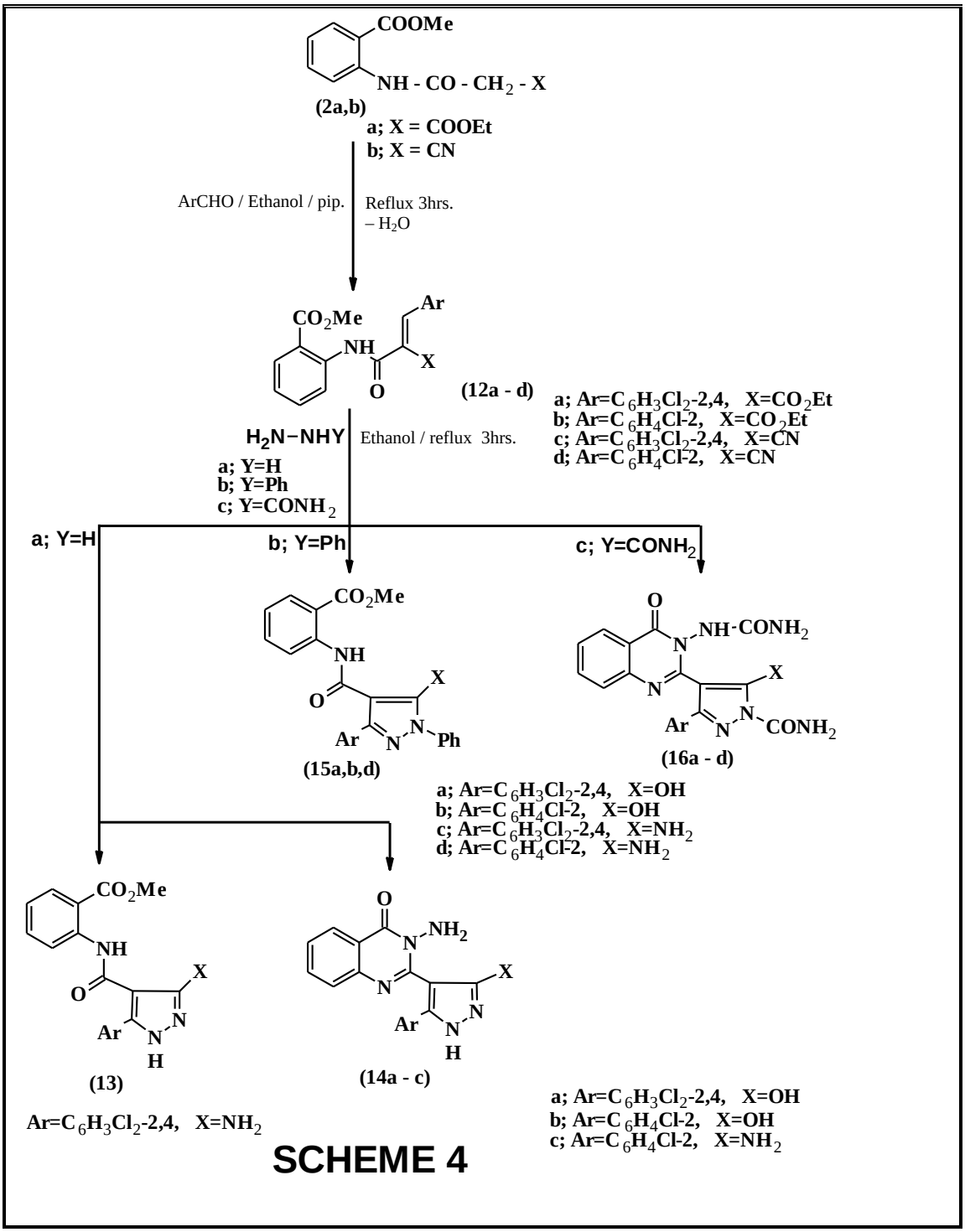


a; Ar=$C_6H_3Cl_2$-2,4, X=$CONH_2$
b; Ar=C_6H_4Cl-2, X=$CONH_2$
c; Ar=$C_6H_4N(CH_3)_2$-4, X=$CONH_2$
d; Ar=C_6H_4Cl-2, X=CO_2Et
e; Ar=$C_6H_4N(CH_3)_2$-4, X=CO_2Et

SCHEME 3

The reactivity of the Substituted-2-methoxycarbonyl acetanilide (**2a,b)** towards some electrophiles was investigated, thus (**2a,b)** were condensed with aromatic aldehydes in ethanolic piperidine mixture and gave the

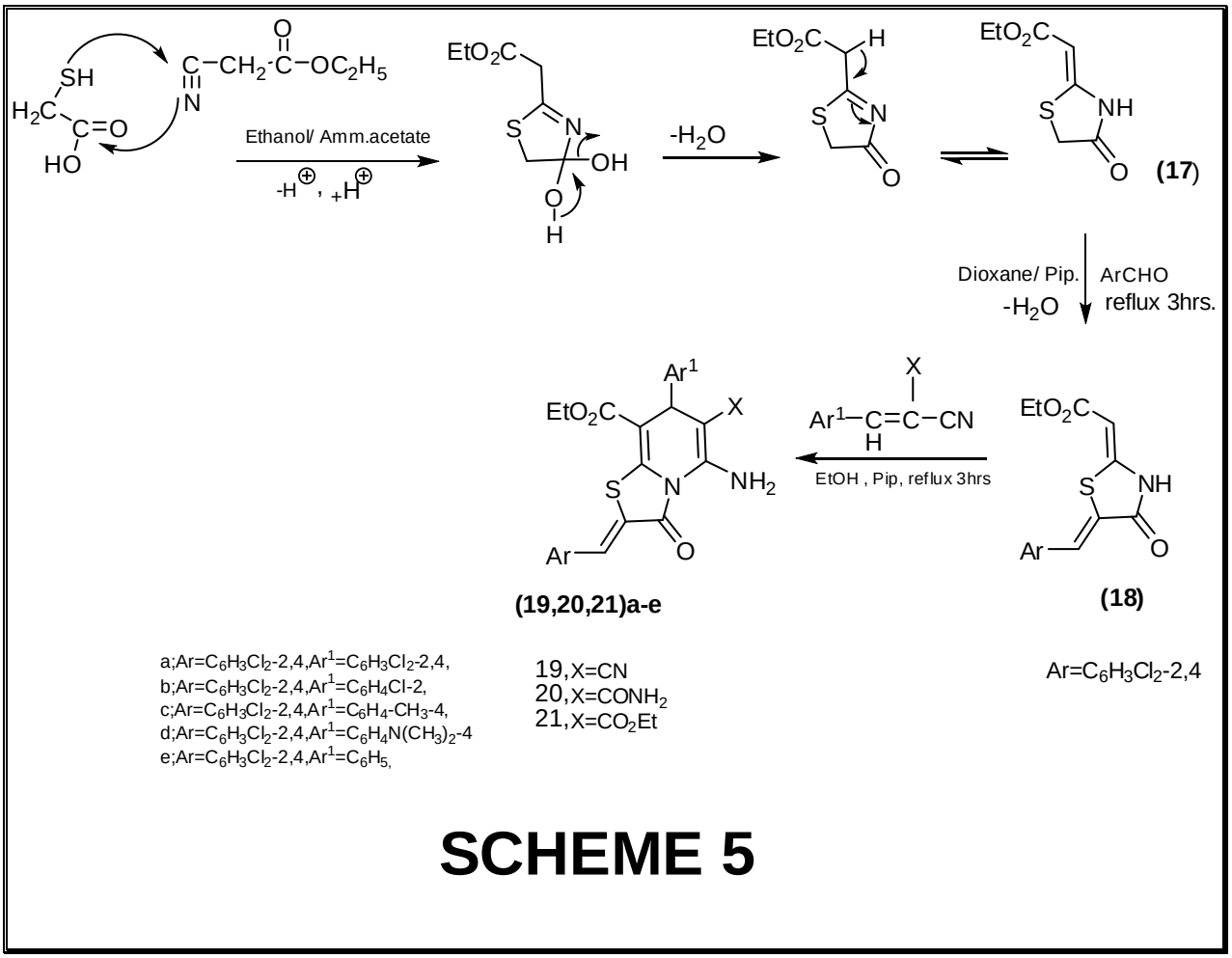
corresponding methyl 2-(substituted -3- arylacrylamido) benzoate **(12a-d)** ;**Scheme4**. The reaction of (**12a-d)** with hydrazine derivatives and semicrbazide as (binucleophiles) in refluxing ethanol afforded the novel heterocycles (**13**, **14a-c**, **15a,b,d** and **16a-d)** ,respectively, **Scheme4**.



SCHEME 4

The second part of our work was interested with synthesis of 4-thiazolidinone derivatives , therefore, the starting material 2-ethoxy carbonyl ethylene-4-thiazolidinone **(17)** was synthesized via cyclocondensation of ethyl cyanoacetate **(1b)** where x = CN with thioglycollic acid in refluxing ethanol in the presence of ammonium acetate ; **Scheme 5**. It was noted that compound (**17)** includes two active methylene groups, the first group is endocyclic and adjacent to the carbonyl group, while the second group is emanating at position-2 and adjacent to the endocyclic amino group. Thus, the reactivity of (**17)** towards some electrophiles was investigated. Thus, treatment of (**17)** with 2,4-dichlorobenzaldehyde in dioxane catalyzed with piperidine at reflux temperature yielded the ethyl-5-(arylmethylene)-4-oxothiazolidin-2-ylidene)acetate derivative **(18)**.

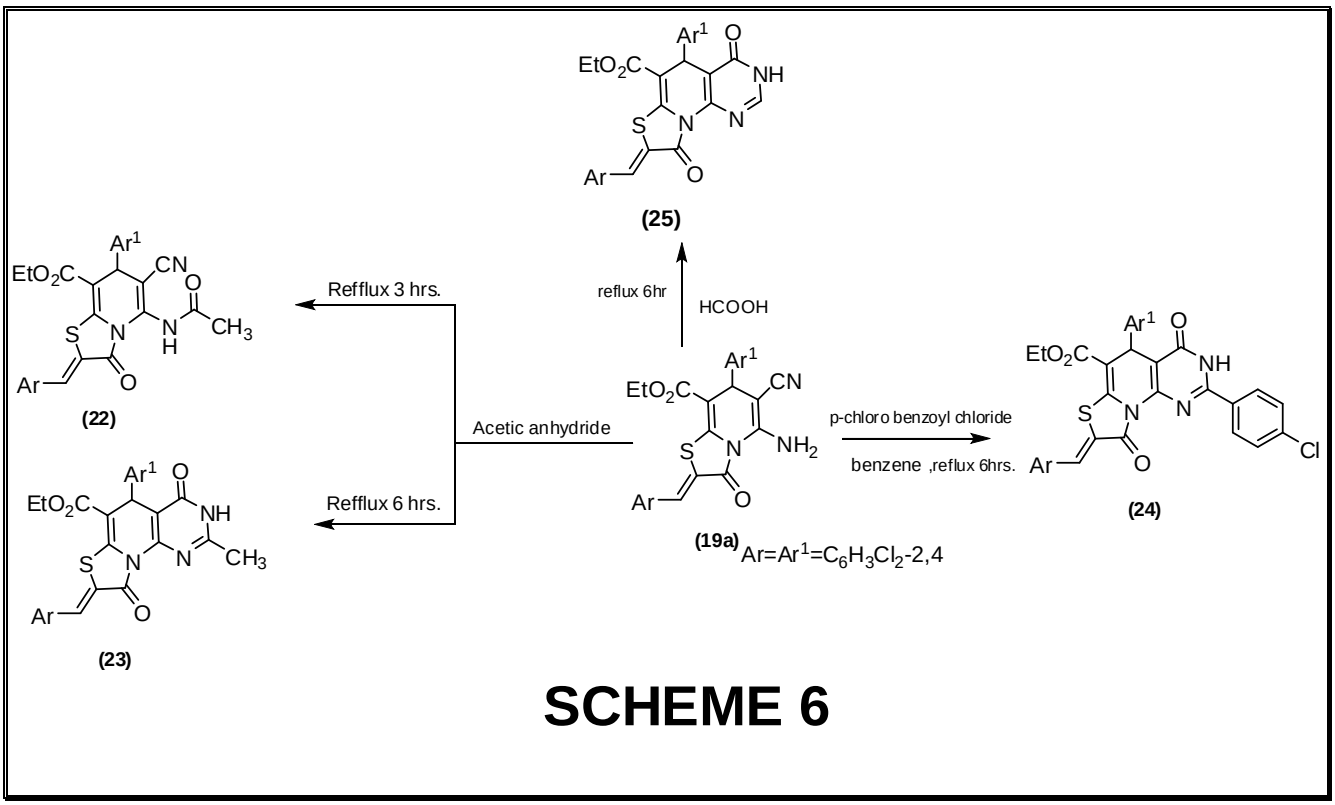
Cyclocondensation of ethyl-5-(arylmethylene)-4-oxothiazolidin-2-ylidene)acetate derivative **(18)** with appropriate α-substituted cinnamonitriles at reflux temperature in ethanol having catalytic amounts of piperidine afforded the corresponding thiazolo[3,2-a] pyridines(**19,20,21)a-e** , respectively ; **Scheme 5.**



SCHEME 5

Reactivety of compound **(19a)** which contains activated ortho aminonitrile and chalcone moieties, wase investigated. Thus, reaction of (**19a)** with acetic anhydride gave the corresponding *N*-acetyl amino

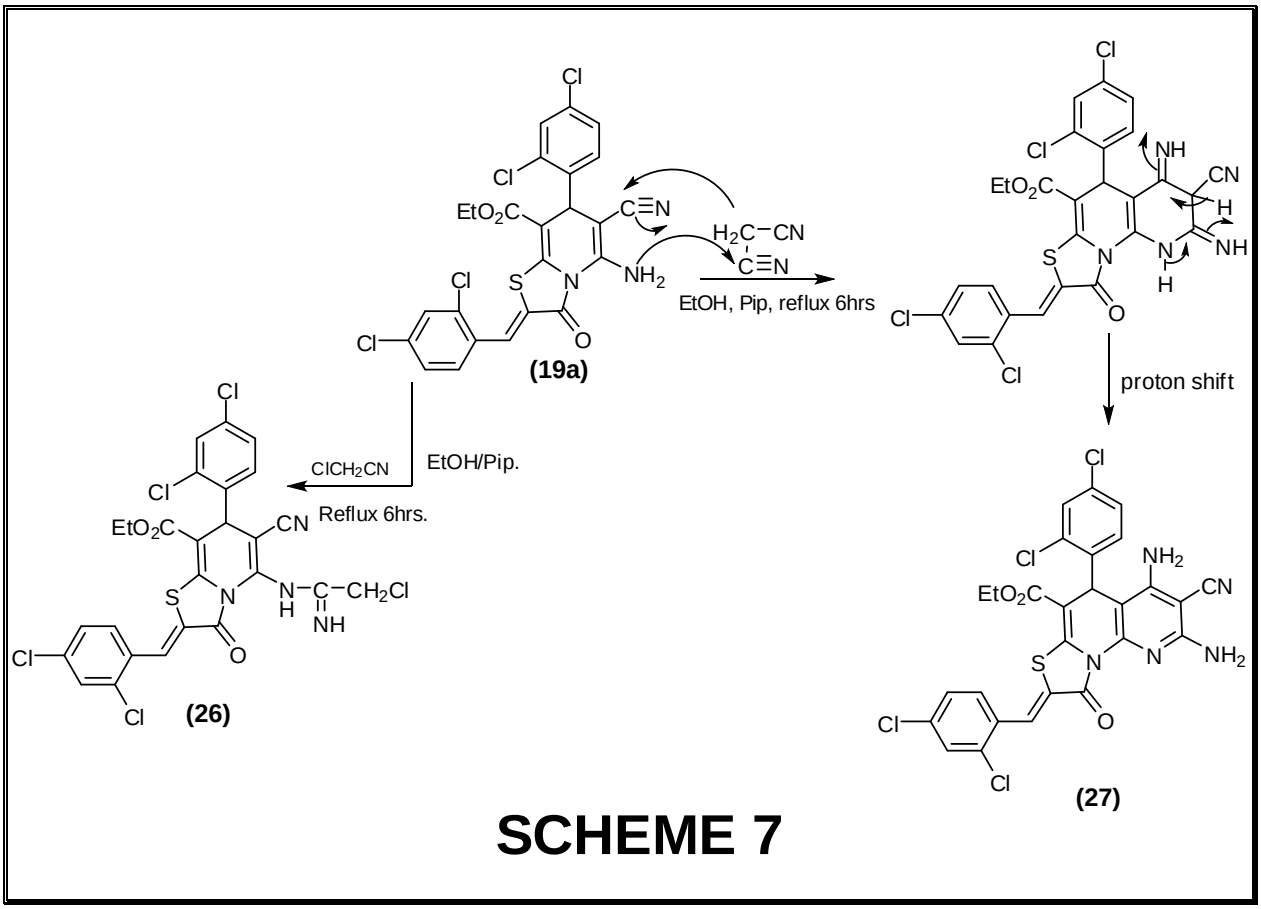
thiazolo [3,2-a] pyridine **(22)** and with 1,8-naphthyridine derivative **(23)** depending on the time of reflux. Also, treatment of (**19a)** with p-chlorobenzoyl chloride and / or HCO_2H gave the corresponding naphthyridine derivatives **(24, 25). Scheme 6.**



SCHEME 6

The present work was extended to investigate the behavior of chloroacetonitrile and /or malononitrile towards **(19a)** in presence of refluxing ethanol piperidine solution, Thus, in case of chloroacetonitrile the product was proved as amidine derivatives **(26)** through the addition

of of NH_2 group of **(19a)** to the nitrile moiety, but in case of malononitrile concerted cyclic addition takes place to furnish thiazolo[3,2-a]-1,8-naphthyridine **(27)** derivative ; **Scheme 7**



SCHEME 7

Stirring of **(19a)** with ethyl isothiocyanate , at room temperature in presence of DMF/ NaOH mixture gave the corresponding thiourea derivative **(28)** . Also, Treatment of (**19a)** with hydrazines (binucleophile) in absolute ethanol under reflux afforded the