SYNTHESIS AND REACTIONS OF SOME HETEROCYCLES CONTAINING NITROGEN AND SULPHUR

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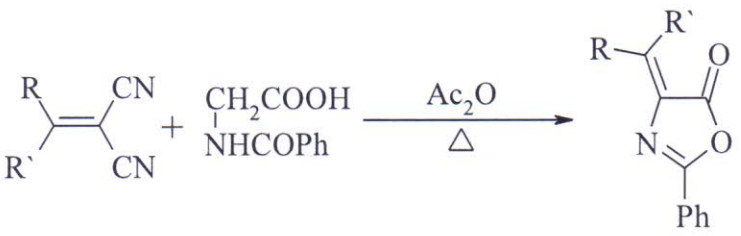
SUMMARY

Part I

A Novel Synthesis of 4-Ylidene-5(4H)- oxazolones Via Trans Olefination and Some Reactions of the Newly Synthesized Derivatives

In this work, efforts have been directed toward developing new synthetic routes for synthesis of 4-substituted-2-phenyl oxazolones as precursors to variety of azole and azine derivatives of expected biological activities. The newly synthesized derivatives were obtained on subjecting the 5-oxzaolones to ring transformation under varieties of reagents and reaction conditions which could effect their rearrangements.

A new facial route for synthesis of 4-arylideneoxazolones **2a-m** is presented. In this methodology, arylmethylene malononitriles **1** were utilized as a trans-arylidene reagent on their reaction with hippuric acid. The reaction sequence takes place via Tandem Michael addition/retro Michael reaction with extrusion of malononitrile. The procedure constitutes a general fashion since the reaction was amenable to a variety of ylidene malononitriles extended from that derived from aromatic aldehydes to that derived from acyclic and cyclic ketones and ketoesters.

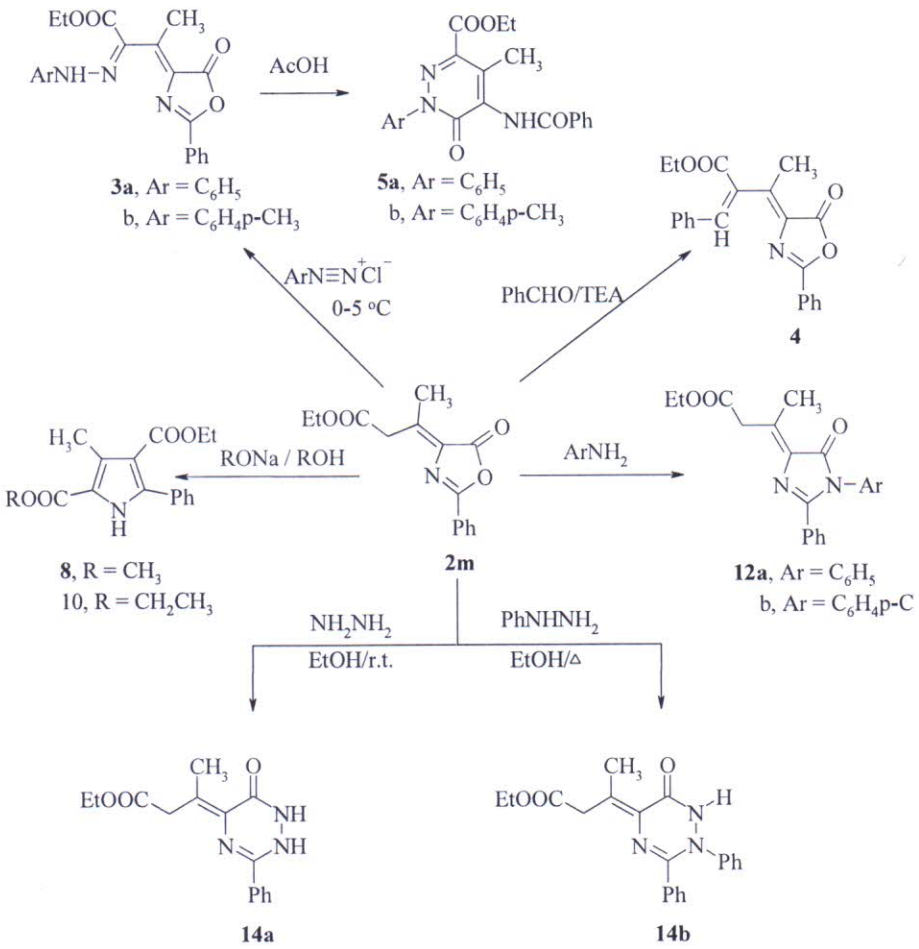


1 **2a-m**

Products	R	R`	Products	R	R`
2a	C_6H_5	H	2h	p-$CH_3C_6H_4$	CH_3
2b	p-$OCH_3C_6H_4$	H	2i	p-ClC_6H_4	CH_3
2c	p-$CH_3C_6H_4$	H	2j	2-thiophenyl	CH_3
2d	p-ClC_6H_4	H	2k	CH_3	CH_3
2e	2-furyl	H	2l	Cyclohexyl	
2f	2-thiophenyl	H	2m	CH_3	CH_2CO_2Et
2g	C_6H_5	CH_3			

The reactions of **2m** with electrophilic and nucleophilic reagents have been studied, thereby several ring transformations occur. Compound **2m** couples smoothly with diazotized aromatic amines in cold ethanolic sodium acetate solution and gave oxazolones **3a, b**. Also, compound **2m** was condensed with benzaldehyde in molar ratio 1:1 in the presence of triethylamine, under fusion condition, to give the oxazolone derivative **4**.

On boiling compounds **3a, b** in acetic acid they underwent ring transformation and affording the pyridazine derivatives **5a, b**. The methanolysis or ethanolysis of 3-(5-oxo-2-phenyl-oxazol-4-ylidene)-butyric acid ethyl ester **2m** in the presence of catalytic amount of sodium methoxide or ethoxide afforded **8** and **10** respectively. The reaction of compound **2m** with nitrogen nucleophiles also has been studied. Thus, the reaction of **2m** with primary aromatic amines, the imidazole derivatives **12a, b** were obtained. Moreover, in the reaction of the oxazolone derivative **2m** with equimolar amount of hydrazine hydrate (in ethanol at room temperature) or phenyl hydrazine (in boiling ethanol) gave the triazines **14a, b** respectively (Scheme 1).

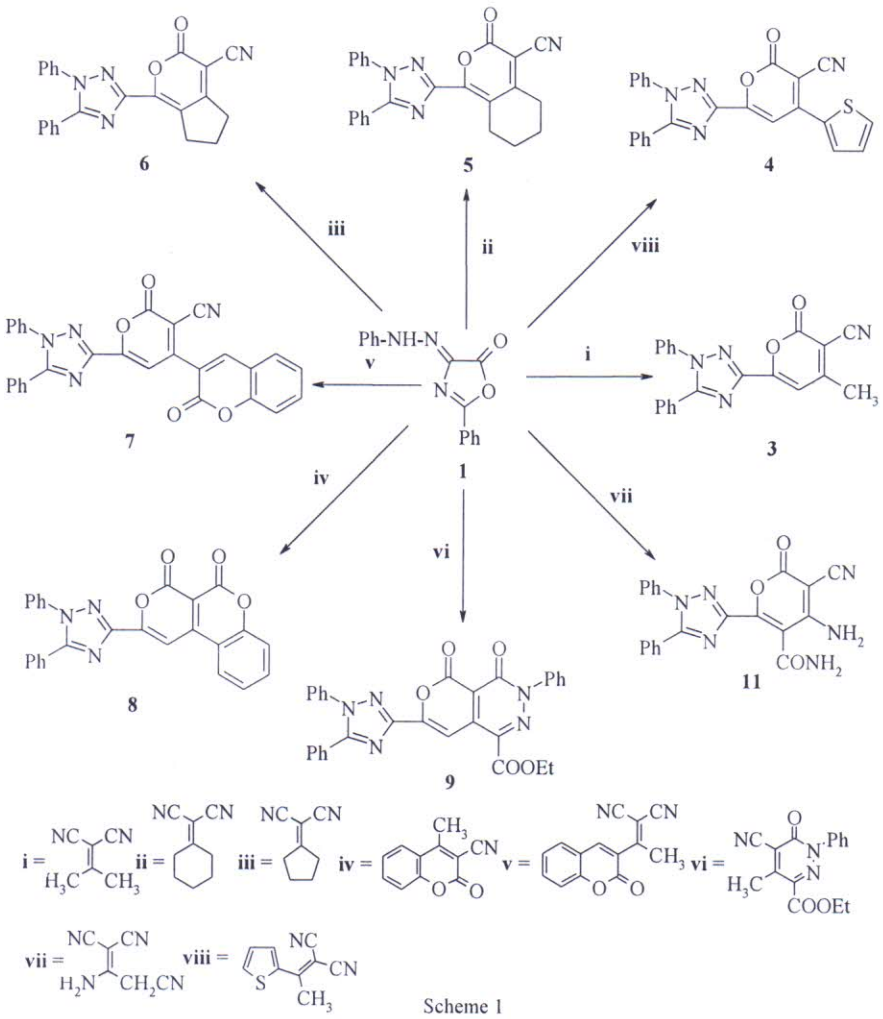

EtOOC
CH3
ArNH–N
O
N
O
Ph
AcOH
COOEt
CH3
N
Ar–N
NHCOPh
O
3a, Ar = C6H5
b, Ar = C6H4p-CH3
5a, Ar = C6H5
b, Ar = C6H4p-CH3
ArN≡N+Cl−
0-5 °C
PhCHO/TEA
Ph–C
H
4
H3C
COOEt
ROOC
N
H
Ph
RONa / ROH
2m
ArNH2
12a, Ar = C6H5
b, Ar = C6H4p-C
N–Ar
8, R = CH3
10, R = CH2CH3
NH2NH2
EtOH/r.t.
PhNHNH2
EtOH/Δ
NH
14a
14b

Scheme 1

Part II

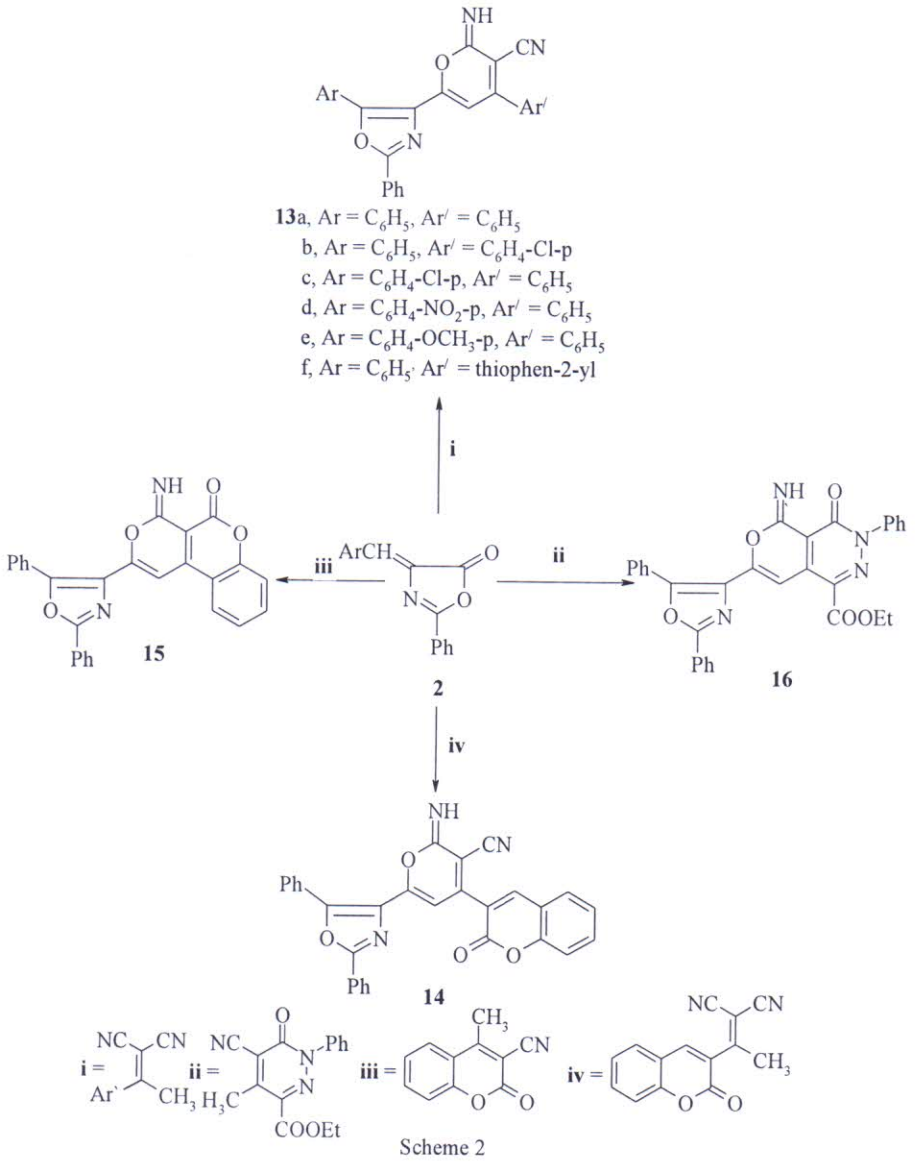
Reactions of 4-Substituted Oxazolones with α,β-Unsaturated Nitriles: A Novel Synthesis of 1,2,4-Triazol-3-yl Pyrans, Oxazol-4-yl Pyrans and Their Annulated Derivatives

2-Phenyl-4-phenylhydrazono-4H-oxazol-5-one **1** reacts with 2-(propan-2-ylidene)-malono-nitrile, 2-(1-thiophen-2-yl-ethylidene)-malononitrile, 2-cyclohexylidene-malononitrile, 2-cyclopentylid-ene-malononitrile, 2-(1-(2-oxo-2H-chromen-3-yl)-ethylidene)malononitrile, 3-cyano-4-methyl coumarin, 5-cyano-4-methyl-6-oxo-1-phenyl-1,6-dihydro-pyridazine-3-carboxylic acid ethyl ester or 2-aminoprop-1-ene-1,1,3-tricarbo-nitrile in sodium/ dry dioxane to yield 1,2,4-triazol-3-yl-pyran derivatives **3-11** respectively (Scheme 1).



Scheme 1

Also, 4-arylmethylene-2-phenyl-4H-oxazol-5-ones **2** react with activated nitriles namely 2-(1-aryl-ethylidene)-malononitrile, 2-(1-(2-oxo-2H-chromen-3-yl)ethylidene)-malononitrile, 3-cyano-4-methyl-coumarin or 5-cyano-4-methyl-6-oxo-1-phenyl-1,6-dihydro-pyridazine-3-carboxylic acid ethyl ester in sodium/dry dioxane to yield 5-aryl-2-phenyloxzaol-4-yl-pyran derivatives **13-16** respectively (Scheme 2).



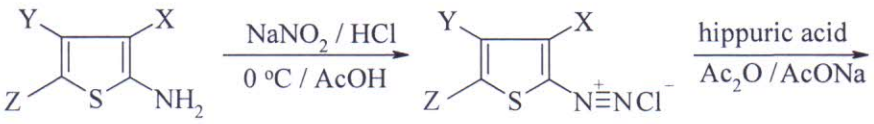
13a, Ar = C_6H_5, Ar/ = C_6H_5
b, Ar = C_6H_5, Ar/ = C_6H_4-Cl-p
c, Ar = C_6H_4-Cl-p, Ar/ = C_6H_5
d, Ar = C_6H_4-NO_2-p, Ar/ = C_6H_5
e, Ar = C_6H_4-OCH_3-p, Ar/ = C_6H_5
f, Ar = C_6H_5, Ar/ = thiophen-2-yl

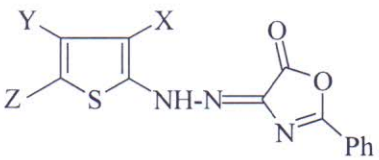
Scheme 2

Part III

Synthesis and Reactions of Some New 2-Phenyl-4-(Substituted Thiophen-2-yl-hydrazono)-4H-Oxazol-5-ones

Diazotization of 2-amino-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxylic acid ethyl ester, 2-amino-5,6-dihydro-4H-cyclopenta-[b]thiophene-3-carboxylic acid ethyl ester or 2-amino-4-aryl-thiophene-3-carbonitrile with sodium nitrite/HCl yielding the diazonium salts which on treating with hippuric acid/acetic anhydride mixture in the presence of sodium acetate trihydrate affording the 2-phenyl-4-(substituted thiophen-2-yl-hydrazono)-4H-oxazol-5-ones **1a-d**.

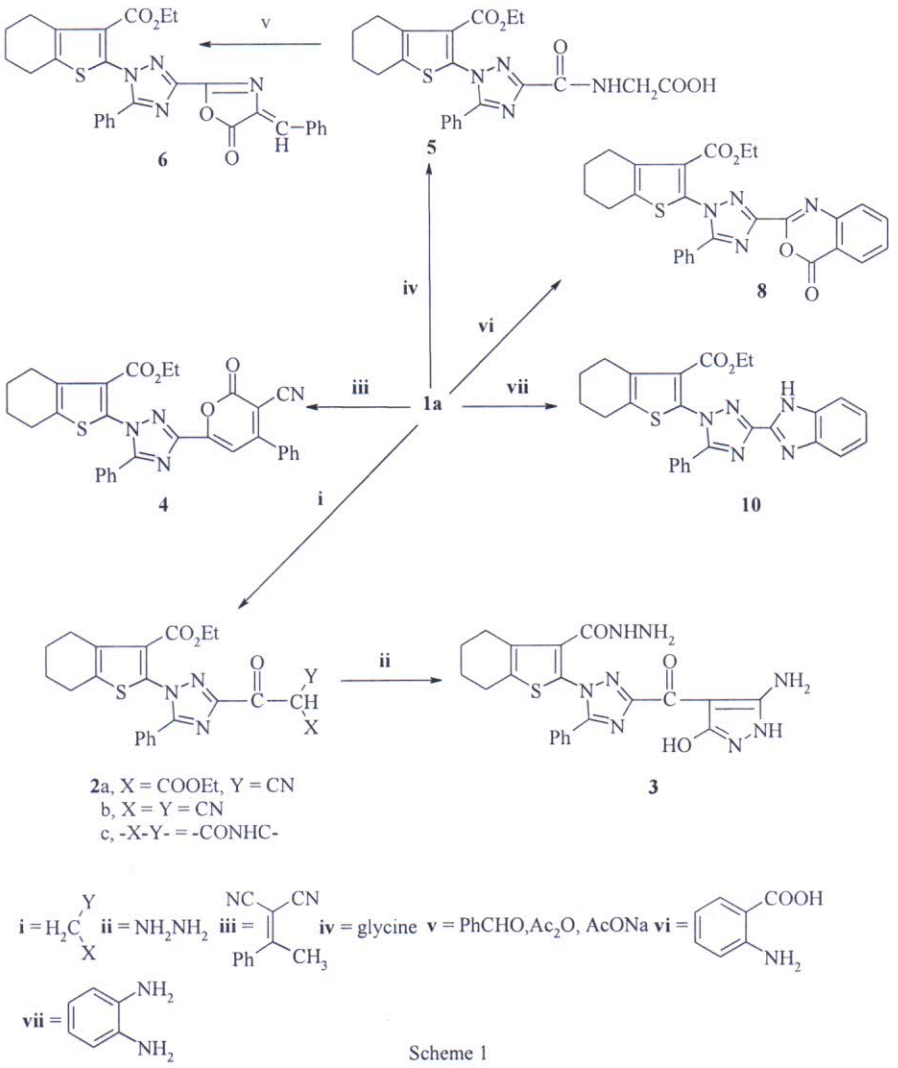




1a, X = CO_2Et, Y-Z = -$(CH_2)_4$-
b, X = CO_2Et, Y-Z = -$(CH_2)_3$-
c, X = CN, Y = C_6H_5, Z = H
d, X = CN, Y = C_6H_4-OCH_3p, Z = H

Oxazolone **1a** reacts with some active methylene namely ethyl cyanoacetate, malononitrile or 5-methyl-2,4-dihydro-pyrazol-3-one in sodium/ dry dioxane to afford the 1,2,4-triazol-3-oynitriles **2a-c** respectively. When **2a** was refluxed with hydrazine hydrate, the pyrazole derivative **3** was obtained. Also, on reacting compound **1a** with 2-(1-phenyl-ethylidene)-malononitrile in sodium/dry dioxane affording the pyranone derivative **4**. Compound **1a** reacts with glycine in boiling acetic acid to afford, through ring transformation, the N-substituted glycine derivative **5**, which on condensing with benzal-dehyde in the presence of acetic anhydride and catalytic amount of

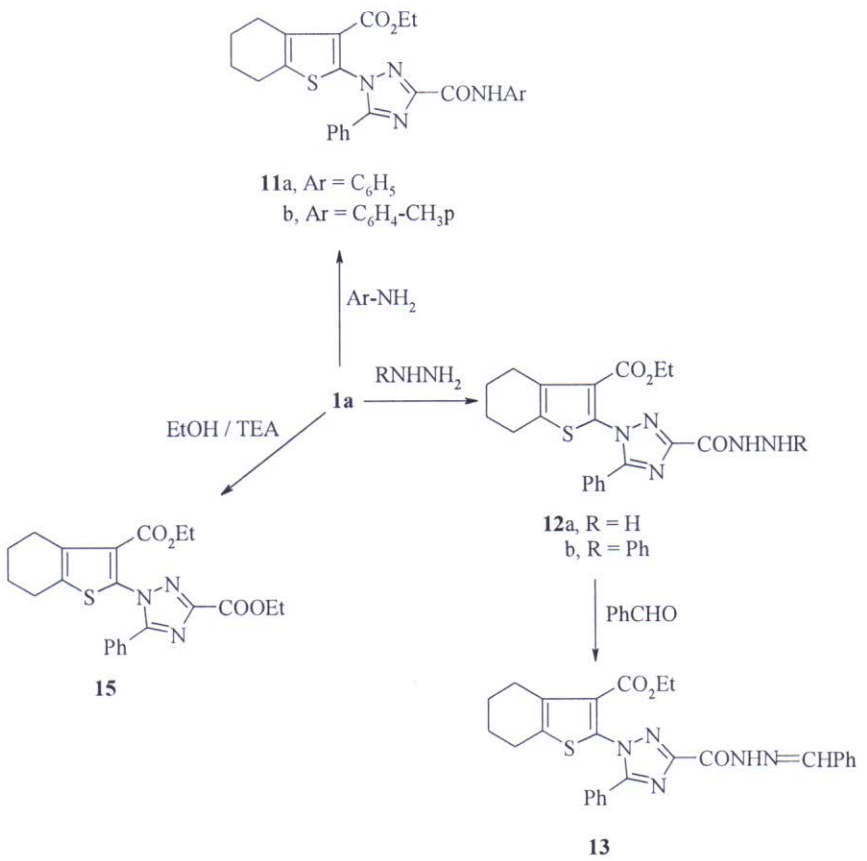
sodium acetate, the oxazolone derivative **6** was obtained. Treatment of **1a** with anthranilic acid or o-phenelyenediamine in boiling acetic acid, yielding the benzoxazine derivative **8** and the benzoimidazole **10** respectively (Scheme 1).



Scheme 1

Also, on the reaction of **1a** with primary aromatic amines namely aniline or p-toludine in boiling ethanol afforded the amide **11a, b** respectively. The reaction of **1a** and hydrazines namely hydrazine

hydrate (at room temperature) and phenyl hydrazine (in boiling ethanol) yielding the hydrazides **12a, b** respectively. Condensation of compound **12a** with benzaldehyde was carried out in ethanol at reflux temperature giving the Schiff's base **13**. On boiling oxazolone **1a** in ethanol containing catalytic amount of triethyl amine afforded the triazole ester **15** (Scheme 2).



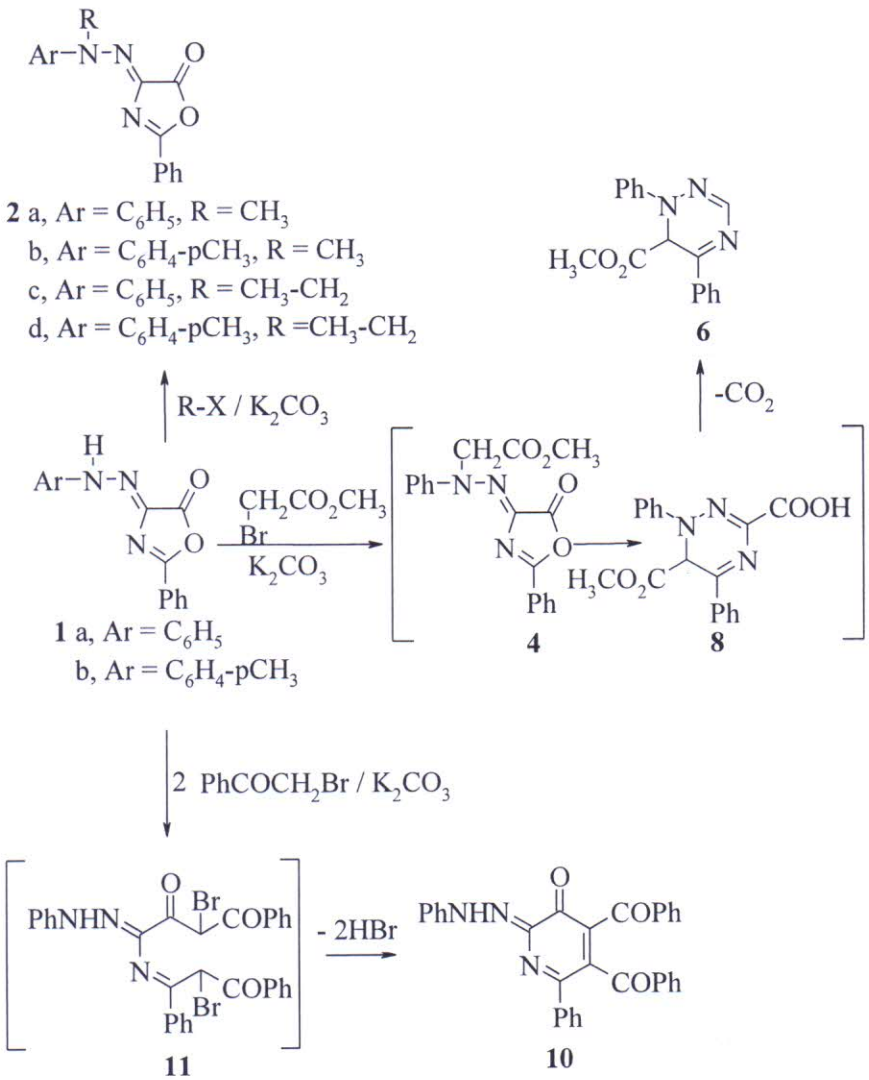
Scheme 2

Part IV

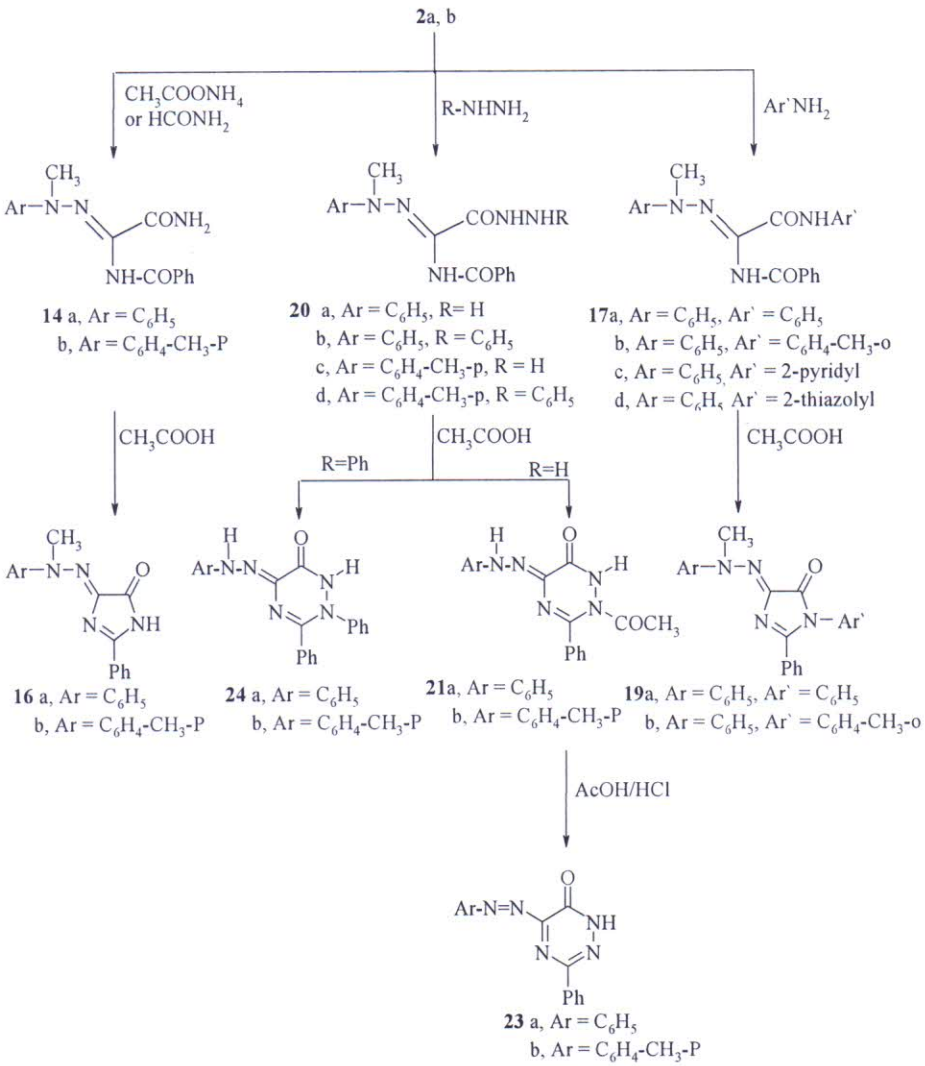
Synthesis and Some Reactions of 4-(2-alkyl-2-arylhydrazono)-2-Phenyloxazol-5-one Derivatives

A series of new 4-(2-alkyl-2-arylhy-drazono)-2-phenyloxazol-5-ones derivatives **2a-d** were synthesized by reaction of the oxazolones **1a, b** with methyl or ethyl iodides. On the other hand trial to alkylate **1a** with methyl bromoacetate or phenacyl bromide afforded the triazine **6** and pyridinone **10** respectively (Scheme 1).

The reaction of **2a, b** with ammonia, primary aromatic amines or hydrazines gave the acyclic amides **14a, b, 17a-d** and hydrazides **20a-d** respectively. Cyclization of **14a, b** and **17a, b** gave imidazoles **16a, b,** and **19a, b** respectively. While cyclization of **20a-d** afforded triazines **21a, b** and **24a, b**. Boiling compounds **21a, b** in acetic acid containing concentrated HCl affording the triazinone derivatives **23a, b** (Scheme 2).


2 a, Ar = C6H5, R = CH3
b, Ar = C6H4-pCH3, R = CH3
c, Ar = C6H5, R = CH3-CH2
d, Ar = C6H4-pCH3, R =CH3-CH2
R-X / K2CO3
1 a, Ar = C6H5
b, Ar = C6H4-pCH3
CH2CO2CH3
Br
K2CO3
4
8
6
-CO2
2 PhCOCH2Br / K2CO3
11
- 2HBr
10

Scheme 1


2a, b
CH3COONH4 or HCONH2
R-NHNH2
Ar`NH2
CONH2
CONHNHR
CONHAr`
NH-COPh
14 a, Ar = C6H5
b, Ar = C6H4-CH3-P
20 a, Ar = C6H5, R= H
b, Ar = C6H5, R = C6H5
c, Ar = C6H4-CH3-p, R = H
d, Ar = C6H4-CH3-p, R = C6H5
17a, Ar = C6H5, Ar` = C6H5
b, Ar = C6H5, Ar` = C6H4-CH3-o
c, Ar = C6H5, Ar` = 2-pyridyl
d, Ar = C6H5, Ar` = 2-thiazolyl
CH3COOH
R=Ph
R=H
16 a, Ar = C6H5
b, Ar = C6H4-CH3-P
24 a, Ar = C6H5
b, Ar = C6H4-CH3-P
21a, Ar = C6H5
b, Ar = C6H4-CH3-P
19a, Ar = C6H5, Ar` = C6H5
b, Ar = C6H5, Ar` = C6H4-CH3-o
AcOH/HCl
23 a, Ar = C6H5
b, Ar = C6H4-CH3-P

Scheme 2