A study on some oxygen or nitrogen heterocyclic ketones with expected biological activities

Thesis Submitted by

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2013

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B. Sc. (Chemistry)

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ACKNOWLEDGMENT

I would like to express my sincere gratitude and indebtedness to **Prof. Dr.M. A.I. Salem, professor of organic chemistry, faculty of science, Ain Shams University,** he was always kind enough to **s**uggest the lines of research and follow the progress of the work with keen interest, guidance and valuable criticism. I would like to thank his for making the chemicals available.

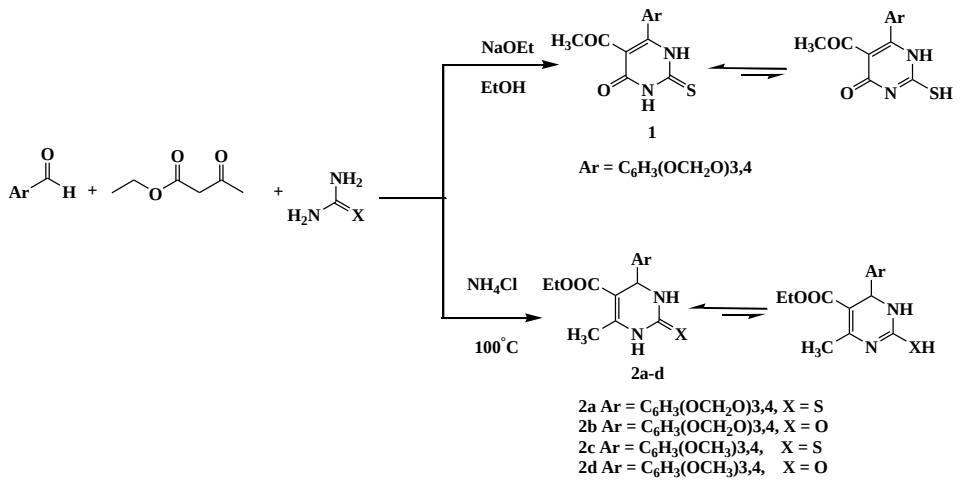
I am deep indebted to **Associate Professor Dr. M.I. Marzouk, Associate Prof. of organic chemistry, faculty of science, Ain shams university,** she was always kind ,helpful, encouragment, meticulous supervision and continuous advice .

Also, I give all my thanks and regards to **Dr. M. S. Salem lecturer of organic chemistry, faculty of science, Ain shams university,** she was not only active enough during the progress of the work but also was loyally cooperative

Finally, my great and deep gratitude for my family, friends, my colleagues in the laboratory and for all people who help me to finish this work.

Summary

Tetrahydropyrimidinone and tetrahydropyrimidinethione derivatives have broad biological activities as antibacterial, antiviral, anti-tumor, antihypertensive. Condensation of aldehydes, ethyl acetoacetate and thiourea or urea using sodium ethoxide or piperidine as a catalyst gave 5-acetyl thioxodihydropyrimidine derivative **1**, while carrying out the reaction in NH_4Cl as a catalyst under solvent-free condition at 100˚C gave ethyl 1,2,3,4-tetrahydropyrimidine-5-carboxylate derivatives **2a-d**.



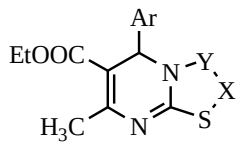
Scheme1

The alkylated derivatives **3-6** named ethyl 6-(benzo [d][1,3]dioxol-5-yl)-2-(ethylthio)-4-methyl-1,6-dihydropyr-imidine-5-carboxylate **3a**, ethyl 6-(3,4-dimeth-oxyphenyl)-2-(ethylthio)-4-methyl-1,6-dihydro-pyrimidine-5-carboxylate **3b,** ethyl 5-(benzo[d][1,3]dioxol-5-yl)-2-imino-7-methyl-3,5-di-hydro-2*H*-thiazolo[3,2-a]pyrimidine-6-carboxylate **4,** ethyl 6-(benzo[d][1,3]dioxol-5-yl)-1-(3-chloro-2-hyd-roxypropyl)-2-

mercapto-4-methyl-1,6-dihydro-pyrimidine-5-carboxylate **5,** ethyl 1-acetyl-6-(benzo[d][1,3]dioxol-5-yl)-4-methyl-2-thioxo-1,2,3,6-tetrahydropyrimidine-5-carboxylate **6** were synthesized from the reaction of tetrahydropyrimidine **2a,c** with mono halogenated compounds such as ethyl iodide, chloro-acetonitrile, epichlorohydrin, acetyl chloride/or acetic anhydride.

Reaction of the pyrimidinethiones **2a,c** with various bifunctional centers, such as ethyl bromoacetate, chloroacetyl chloride and chloroacetic acid in K_2CO_3 or DMF afforded the same cyclic sole products namely ethyl 5-aryl-7-methyl-3-oxo-3,5-dihydro-2*H*-thiazolo[3,2-α]pyrimidine-6-carbo-xylate **7a,b** which condensed with p-fluorobenzaldehyde in the presence of a mixture of acetic acid, acetic anhydride and sodium acetate to afford 3,3'-[(4-fluorophenyl)methylene]bis-[ethyl 5-(benzo[d][1,3]dioxol-5-yl)-7-methyl-3-oxo-3,5-dihydro-2H-thiazolo [3,2-a]pyrimidine -6-carboxylate] **11**.

The reaction of pyrimidinethione **2a** with chloroacetyl chloride in KOH or NaOEt afforded ethyl 6-(benzo[d][1,3]dioxol-5-yl)-2-(2-chloroacetylthio)-4-methyl-1,6-dihydropyrimidine-5-carboxylate **8** and the cyclic adduct ethyl 5-(benzo[d][1,3]dioxol-5-yl)-7-methyl-2-oxo-3,5-dihydro -2*H*-thiazolo [3,2-a]pyrimidine-6-carboxylate **9** respectively.

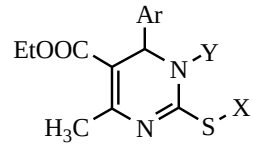


4 X; CH, Y;=NH

7a,b X; CH_2, Y; C=O

9 X; C=O, Y; CH_2

12 X; C=O, Y; C=O

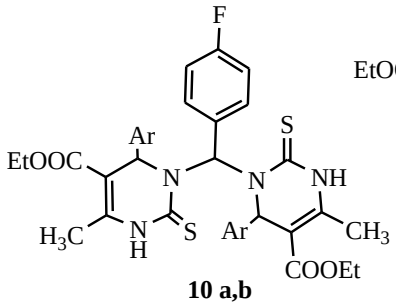


3a,b X; C_2H_5, Y; H

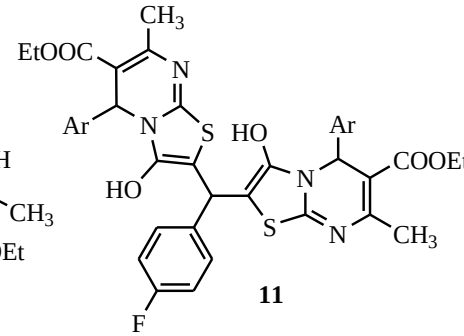
5 X; $CH_2CH(OH)CH_2Cl$, Y; H

6 X; H, Y; $COCH_3$

8 X; $C=OCH_2Cl$, Y; H



10 a,b



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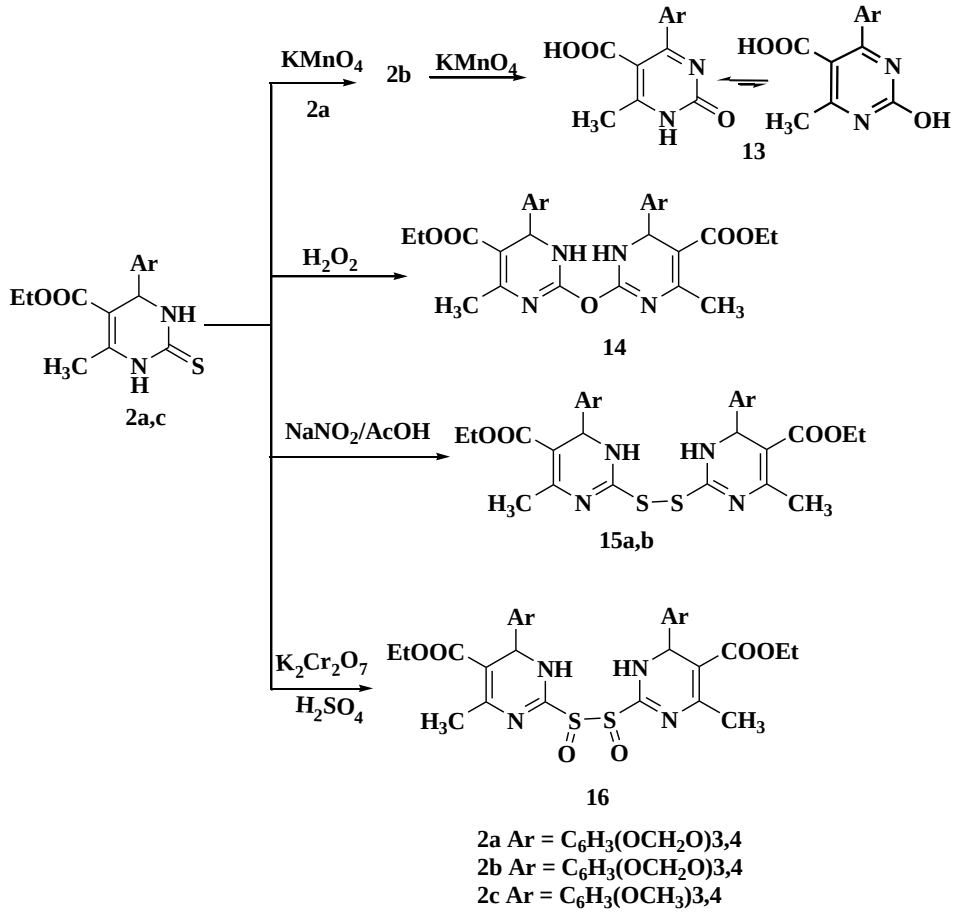
Scheme 2

The condensation of the pyrimidinethione**s 2a,c** and the thiazolo pyrimidine **7a** with p-fluorobenzaldehyde in the presence of acetic acid, acetic anhydride and sodium acetate gave 3,3'-[(4-fluorophenyl)methylene]bis-[ethyl4-aryl-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylat-e]**10a,b**.

The reaction of **2a** with oxalyl chloride in dry benzene afforded ethyl 5-(benzo[d][1,3]dioxol-5-yl)-7-methyl-2,3-dioxo -3,5-dihydro-2*H*-thiazolo[3,2a]pyrimidine-6-carboxylate **12**.

Oxidation of **2a,b** gave different products depending on the oxidizing agents that used such as potassium permanganate solution, hydrogen peroxide, sodium nitrite, or potassium

dichromate to give compound **2b**, and 4-(benzo[d][1,3]dioxol-5-yl)-6-methyl-2-oxo-1,2-dihydropyrimidine-5-carboxylic acid **13**, ethyl 4-(benzo[d][1,3]dioxol-5-yl)-2-(4-(benzo[d][1,3] dioxol-5-yl)-5-(ethoxycarbonyl)-6-methyl-pyrimdin-2-yloxy)-6-methylpyrimidine-5-carboxylate **14**, ethyl 4-aryl-2-(4-aryl)-5-(ethoxycarbonyl)-6-methyl-3,4-dihydropyrimdin-2-yldithio)-6-methyl-3,4-dihydropyrimidine-5-carboxylate **15a,b**, and bis-pyrimidine sulfoxide derivative **16** respectively.



Scheme 3

Reaction of **2a,c** with $POCl_3$/DMF under Vilsmeiere-Haack reaction afforded the 6-aryl-1-formyl-4-(2-oxoethyl-

idene)-2-thioxohexahydropyrimidine-5-carboxylic acid derivatives **17a,b**.

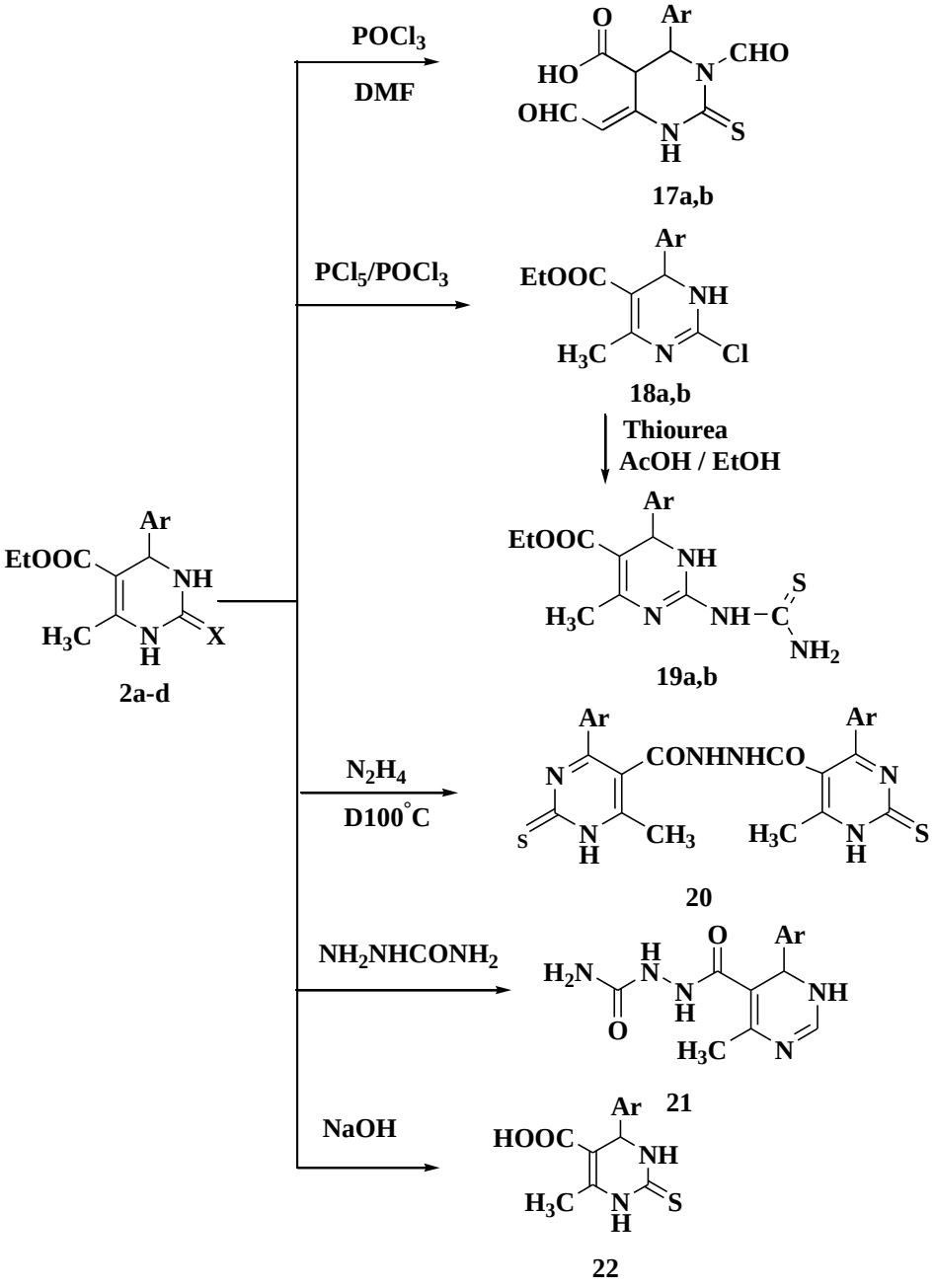
Chlorination of the dihydropyrimidinone **2b,d** with $PCl_5/POCl_3$ mixture afforded the corresponding ethyl 6-aryl-2-chloro-4-methyl-1,6-dihydropyrimidine-5-carboxylate **18a,b** which reacted with thiourea to afford ethyl 6-aryl-4-methyl-2-thioureido-1,6-dihydropyrimidine-5-carboxylate **19a**,**b** respectively.

The pyrimidinethiones **2a** reacted with hydrazine hydrate, semicarbazide hydrochloride, and sodium hydroxide to afford the corresponding compound **20**, 1-(6-(benzo[d][1,3]dioxol-5-yl)-4-methyl-1,6-dihydropyrimidi-ne-5-carbonyl)semi-carbazide **21** and 4-(benzo[d][1,3]dioxol-5-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid **22**.

Antimicrobial, anticancer and antioxidant activities of some compounds were investigated using the standard method against different bacterial, fungal strains, anticancer and antioxidant in comparison with standard drugs and the results shows from moderate to high reactivity.

The synthesized newly products were well established according the following arguments:

a) Elemental analysis
b) Spectroscopic studies. IR, ^{1}H-NMR, ^{13}C-NMR and mass spectra.


POCl3
DMF
17a,b
PCl5/POCl3
18a,b
Thiourea
AcOH / EtOH
19a,b
2a-d
N2H4
D100°C
20
NH2NHCONH2
21
NaOH
22

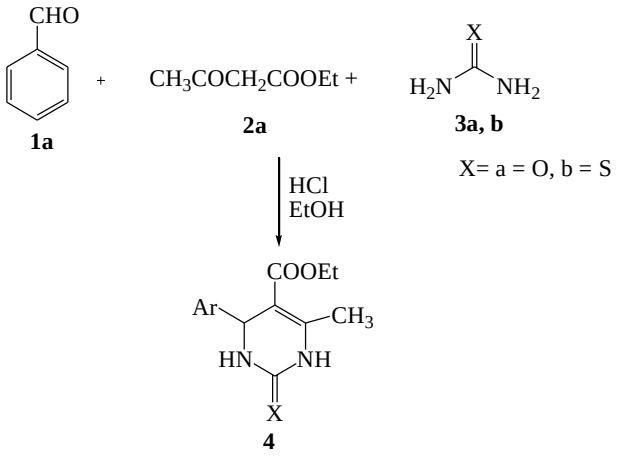
Scheme 4

Synthesis of Pyrimidinone and Pyrimidine thione

1-Biginelli's Reaction:

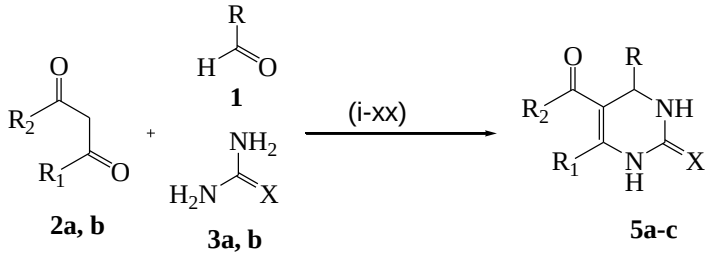
In 1893 Italian chemist Pietro Biginelli reported on the acid-catalyzed cyclocondensation reaction of ethyl acetoacetate, benzaldehyde and urea or thiourea [1]. The reaction was carried out simply by heating a mixture of the three components dissolved in ethanol with a catalytic amount of HCl at reflux temperature. The product of this novel one-pot, three-component synthesis that precipitated on cooling of the reaction mixture was identified correctly by Biginelli as 3,4-dihydropyrimidin-2(1*H*)-one.

The synthetic potential of this new heterocycle synthesis (now known as Biginelli reaction) remained unexplored for quite some time. In the 1970s and 1980s interest slowly increased, and the scope of the original cyclocondensation reaction was gradually extended by variation of all three building blocks, allowing access to a large number of multifunctionalized dihydropyrimidines [26,45,137,112 ,139 ,129 ,92].

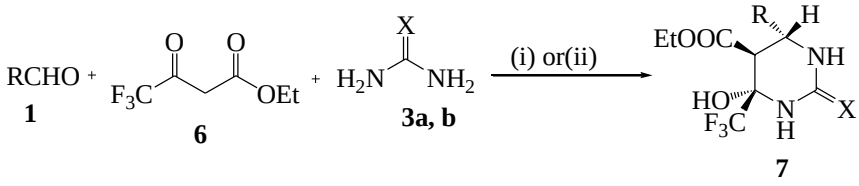


Biginelli's reaction for the synthesis of pyrimidine-2-thiones and their derivatives involved three components, one-pot condensation of a β-ketoesters with an aldehyde and thiourea under strongly acidic conditions [26] and several improved procedures have recently been reported using[13] LiBr, VCl_3, $ZrCl_4$, HPAS (heteropolyacids) [144], $H_3PMO_{12}O_{40}$ [133], IBX(Iodoxy benzoic acid) [131] ,P_2O_5/ $MeSO_3H$[7], calcium sulfate dihydrate [133] ($CaSO_4.2H_2O$), CAN(Ceric ammonium nitrate) [38] , metal phosphate (NaH_2PO_4, KH_2PO_4) [69], PPA(Phenyl phosphonic acid)/CH_3CN [9] ,$CuCl_2.2H_2O$/ HCl[125], $Fe(HSO_4)_3$ [48], $SrCl_2$. $6H_2O$/ HCl[88], SiO_2-Cl[58], , ionic liquid[69], $AlCl_3$/ conc. HCl[49], SBSSA (Silica-bonded-S-sulfonic acid)[94], Amberlyst 15 DR[128], chlorotrimethylsilane [127] (TMSC)/ DMF, [hmim]HSO_4[66], dilute HCl [69] and Cyanuric Chloride[15], as catalyst. However, most of these reactions required expensive reagents, strongly acidic conditions, high

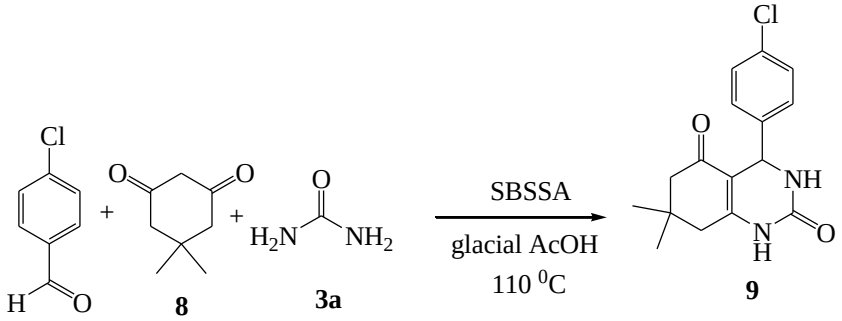
temperatures and moreover, these methods involved three components.



(i) LiBr, CH_3CN,reflux; (ii)VCl_2 / CH_3CN, reflux; (iii) HPAS, AcOH / reflux; (iv) IBX, 60 ^{0}C, H_2O; (v) P_2O_5 / $MeSO_3H$, rt, 5-15 min; (vi) $CaSO_4.2H_2O$; (vii) (CAN) neat, 80-90 ^{0}C; (viii) Metal Phosphate,glacial AcOH, 40-50^{0}C; (ix) PPA / CH_3CN,reflux; (x) $CuCl_2.2H_2O$-HCl,Cround 2-5 min; (xi)$Fe(HSO_4)_3$, CH_3CN, reflux; (xii)$Fe(HSO_4)$,Solvent Free 100 ^{0}C; (xiii) $SrCl_2.6H_2O$, HCl; (xiv) SiO_2-Cl, Solvent Free; (xv)Ionic Liquid,100 ^{0}C,0.5 h; (xvi) $AlCl_3$, Conc. HCl; (xvii) TMSC, DMF; (xviii) SBSSA; (xix)Amberlyst 15 DRY.



(i) $ZrCl_4$, Ethanol, 4-6 h; (ii)Cyanuric Chloride, EtOH



In continuation of the synthesis of fused pyrimidines [72,73], D. Nimalini.[35] reported an efficient and high yielding method for two components, one-pot synthesis of pyrimidine-2-thiones using chromium (III) chloride as catalyst under aqueous conditions, which not only is very