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Synthesis of some Pyrimidine-2-one and Pyrimidine-2-thione Compounds

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ABSTRACT

An efficient synthesis of chalcones (1-7) was achived by condensation of substituted benzaldehyde with substituted acetophenone in ethanolic sodium hydroxide (50%).The chalcones were reacted with urea and thiourea to give the pyrimidinones(8-14) and pyrimidinethiones(15-21) respectively. All the prepared compounds were confirmed by the available physical and spectral methods.

Keywords: pyrimidine-2-one, pyrimidine-2-thione, heterocyclic compound, chalcones.

تحضير بعض مركبات البيريميدين-2-أون والبيريميدين-2-ثايون

الملخص

تم تحضير الجالكونات(1-7) من تكاثف البنزالديهايد المعوض مع الاسيتوفينون المعوض في محلول هيدروكسيد الصوديوم الكحولي(50%). تم مفاعلةالجالكونات المحضرة مع اليوريا والثايوريا لتكوين مركبات البريميدينون (8-14) والبريميدينثايون (15-21) على التوالي. شخصت جميع المركبات المحضرة باستخدام الطرق الفيزياوية والطيفية المتوفرة.

الكلمات الدالة: البريميدينونوالبريميدينثايون، المركبات الحلقية غيرالمتجانسة، الجالكونات.

INTRODUCTION

The hetrocyclic molecules are of biological interest due to their potential physical and chemical properties (Brown,1998). Among these the pyrimidine compounds which occupy aunique position in pharmaceutical chemistry. They are components of nucleic acids. The important pyrimidine compounds have diverse applications as anti-bacterial (Pershin *et al.*,1972), fungicidal (Metolcsy,1971), analgesics (Regnier *et al.*, 1972), anti-inflammatory (Winter *et al.*,1962) and anti-tumor agents (Suguira *et al.*,1973). Nowadays the one step method involving three component condensation using different reagents (Dipti *et al.*, 2010) are popular in synthetic organic chemistry for the synthesis of heterocyclic compounds.They are present in nature and are of great significance to life because their structural subunits exist in many natural products such as vitamins, hormones, antibiotics (Yuhong and Varma, 2006). Hence,they have attracted considerable attention in the design of biologically active molecules.(Kawamoto *et al.*, 2003).A practical method for the synthesis of such compounds is of great interest in synthetic organic chemistry. (Junichi *et al.*, 2000).

The chalcones were synthesized by condensation of different substituted aldehydes withacetophenones (Dhaval and Dhrubo, 2009), through claisen – Schmidt condensation reaction in ethanolic NaOH solution (Vogel, 2006).

Chalcones either natural or synthetic are known to exhibit various biological activities. They have been reported to possess anti-oxidant, anti-leishmanial, anti-inflammatory anti-tumor and anti-bacterial activity. The presence of reactive α,β – unsaturated keto function in chalcone is found to be responsible for their anti microbial activity (Larsen *et al.*, 2005).

Chalcones considered as a precursor of flavonoids and isoflavonoids and they are present in edible plants (stevens *et al.*, 2000) and have also been shown to display a diverse array of pharmacological activities, such as anti- protozoal and antihyperglycemic properties (Liu *et al.*, 2001) (Satyanarayana *et al.*, 2004). In the present research, a series of chalcones was prepared as a synthon to synthesize new pyrimidine and pyrimidine thione compounds.

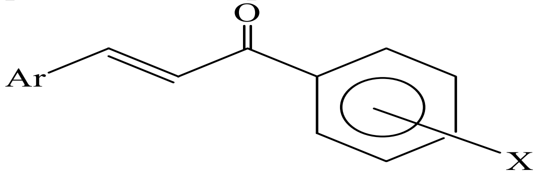
EXPERIMENTAL

Melting points (M.P) were measured on Electrothermal, Gallenkamp melting point apparatus and are uncorrected.Infrared (FTIR) spectra were recorded as (KBr) disc using a Bruker, FT.IR spectrophotometer tensor 27. Ultraviolet (U.V) spectra were performed on shimadzu UV- visible spectrophotometer UV-1650 PC using chloroform as a solvent.

A. Synthesis of 1,3-diaryl-2-propen-1-one (1-7) (Vogel, 1974):

To a stirred and ice cooledsolution of (0.055 mole, 50%) sodium hydroxide in (20 ml) of water and (12.5 ml) of ethanol, a freshly distilled substituted acetophenone (0.043 mole) was added followed by (0.043 mole) of substituted benzaldehyde. The temperature of the mixture was mentained at (20-25°C) with vigorous stirring for (2-3 hours), until the mixture became thick. The mixture was left in the refrigerator overnight. The product was filtered off under vacuum and washed with water until the filterates became neutral to litmus paper, washed with (20 ml) ice-cold ethanol, then recrystalized from ethanol. The physical properties and the spectral data were listed in Table(1).

Table 1: The physical properties and the spectral data for compounds(1-7).

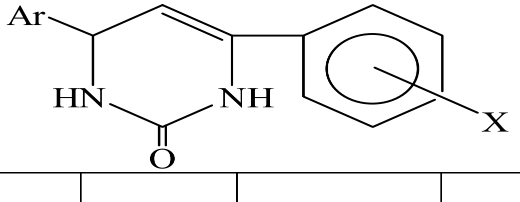


Compd. No.	Ar	X	M.P °C	% yield	UV (CH Cl_3) λ max (nm)	FT.IR (KBr) υ Cm^{-1}	
						C=O	C=C
1	3,4-Dichloro benzaldehyde	p-Br	110-112	85	430	1720	1635
2	3-Indol carbaxaldehyde	p-Br	170-172	68	400	1685	1637
3	9-Anthraldeh yde	p-CH_3	122-124	75	420	1684	1650
4	p-chlorobenzaldehyde	p-Cl	88-90	90	380	1720	1630
5	2-piperenal	p-NO_2	168-170	90	430	1695	1655
6	2-piperonal	p-OMe	118-120	90	420	1720	1635
7	p-Touldehyde	p-OMe	128-130	90	400	1720	1655

B. Synthesis of 3,4-dihydro -4,6-diaryl pyrimidine-2-(1H)-one (8-14)(Vogel, 2006)

To amixture of chalcone(1-7)(0.025 mole) and urea (3.0g,0.05 mole), an aqueous sodium hydroxide solution (30%,15mℓ) and ethanol (75 mℓ) were added with stirring. The mixture was refluxed for (2 hours). The mixture was poured with stirring on (125ml) of water, then allowed to stand for (15 minutes). The mixture was filtered, and the filtrate was cooled in an ice-bath and acidified with concentrated hydrochloric acid. The precipitate was filtered off under reduce pressure then recrystallized from ethanol. The physical and the spectral data were listed in Table (2).

Table2: The physical properties and the spectral data of compounds (8-14).

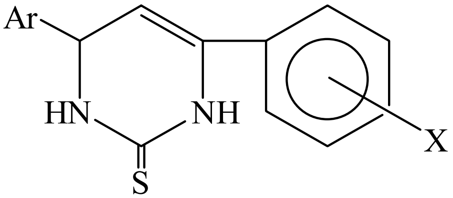


Compd. No.	M.P °C	yield %	UV(CH Cl_3) λ max (nm)	FT.IR (KBr) υ Cm^{-1}		
				C=O	C=C	N-H
8	220	70	320	1676	1630	3400
9	155-157	65	340	1685	1635	3402
10	226-228	50	330	1684	1634	3413
11	118-120	70	320	1675	1630	3442
12	280	50	380	1685	1630	3450
13	230-232	50	350	1672	1625	3446
14	60-62	50	330	1686	1630	3400

B. Synthesis of 3,4-dihydro-4,6- diaryl pyrimidine-2 (1H) thiones (15-21), (Krein *et al.*, 1993).

To a mixture of aqueous sodium hydroxide solution (6 ml, 50%) and benzene (25 ml), tetrabutyl ammonium bromide (TBAB) (0.2g , 0.0015 mole) and thiourea (0.005 mole) were added with stirring (for 5 minutes). To this mixture the chalcone (0.005 mole) was added with stirring. The stirring was continued for 24-72 minutes at 40-60°C. The organic layer was separated and washed several times with water until become clear to remove the catalyst and base, then dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the precipitate was recrystallized from chloroform. The physical and spectral data were listed inTable (3).

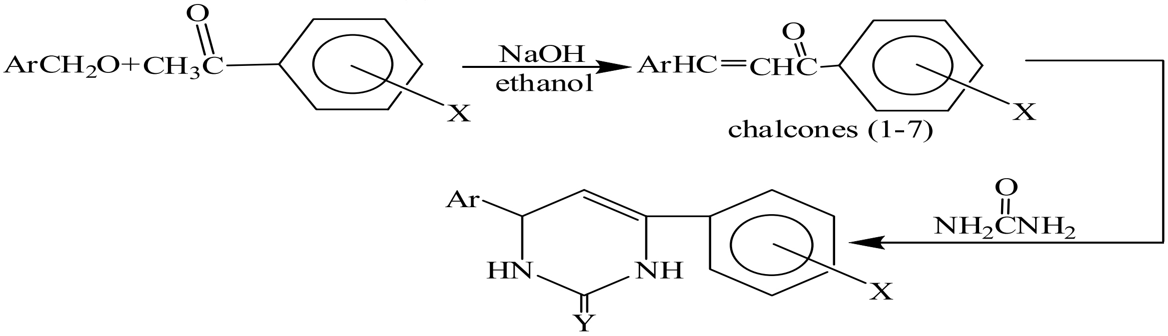
Table3:The physical properties and the spectral data for compounds (15-21).



Compd. No.	M.P °C	% yield	UV (Ethanol) λ max(nm)	Time (min)	Temp °C	FT.IR (KBr) υ Cm^{-1}		
						C=S	C=C	N-H
15	250-252	60	420	48	50-55	1160	1650	3400
16	100-102	70	320	72	45-50	1164	1645	3450
17	230-233	70	330	24	55-60	1165	1657	3420
18	150-152	60	320	48	40-45	1160	1646	3400
19	220-222	70	310	48	55-60	1167	1655	3430
20	160-162	60	330	24	50-55	1162	1654	3450
21	210-212	60	330	72	55-60	1160	1650	3420

RESULT AND DISCUSSION

The carbonyl compounds are considered as a precursor for synthesis of many important heterocyclic compounds, through their reaction with other different compounds. This work involves preparation of chalcones which reacted consequently with urea and thiourea to form the pyrimidine-2-ones, pyrimidine-2-thiones respectively. The synthetic routes are shown in Scheme (1).



Y = O, S

Scheme 1: Synthesis of pyrimidine-2-ones and pyrimidine-2-thiones.

The chalcones (1-7) have been prepared by condensation of aromatic aldehyde with substituted acetophenone under basic conditions (ethanolic sodium hydroxide solution).

The structure of these chalcones was established by spectroscopic methods (Table 1). The FT, IR spectra (KBr disk) (Williams *et al.*, 1973) showed a strong absorption bands at (1720-1684cm^{-1}) for the C=O bondstreaching, and bands at (1655-1630cm^{-1}) for (C=C)bond stretching. The UV spectra (AL-Hajjar *et al.*, 1980) showed maximum absorption at the wave length (λ_{max}) 380-430 nm due to the extension of the π system (Parikh,1974). The condensation of compounds (1-7) with urea under basic conditions (aqueous sodium hydroxide solution) afforded pyrimidine-2-one compounds (8-14). The reaction may be proceed through nucleophilic1,2-addition (Claisen addition) or 1,4-addition (Michael addition) (Scheme 2). According to the theoretical calculations of the heat of formation (H.F), and the steric energy (S.E) (using the semiempirical method, Chem. Office version 2006), the reaction may be proceed via Michael addition. By Michael route the heat of formation and the steric energy of compound 8a are -33.681 and 20.473 Kcal/mole respectively, while their values are -27.751 and 24.250 Kcal/mole respectively for compound 8b (Claisen route).

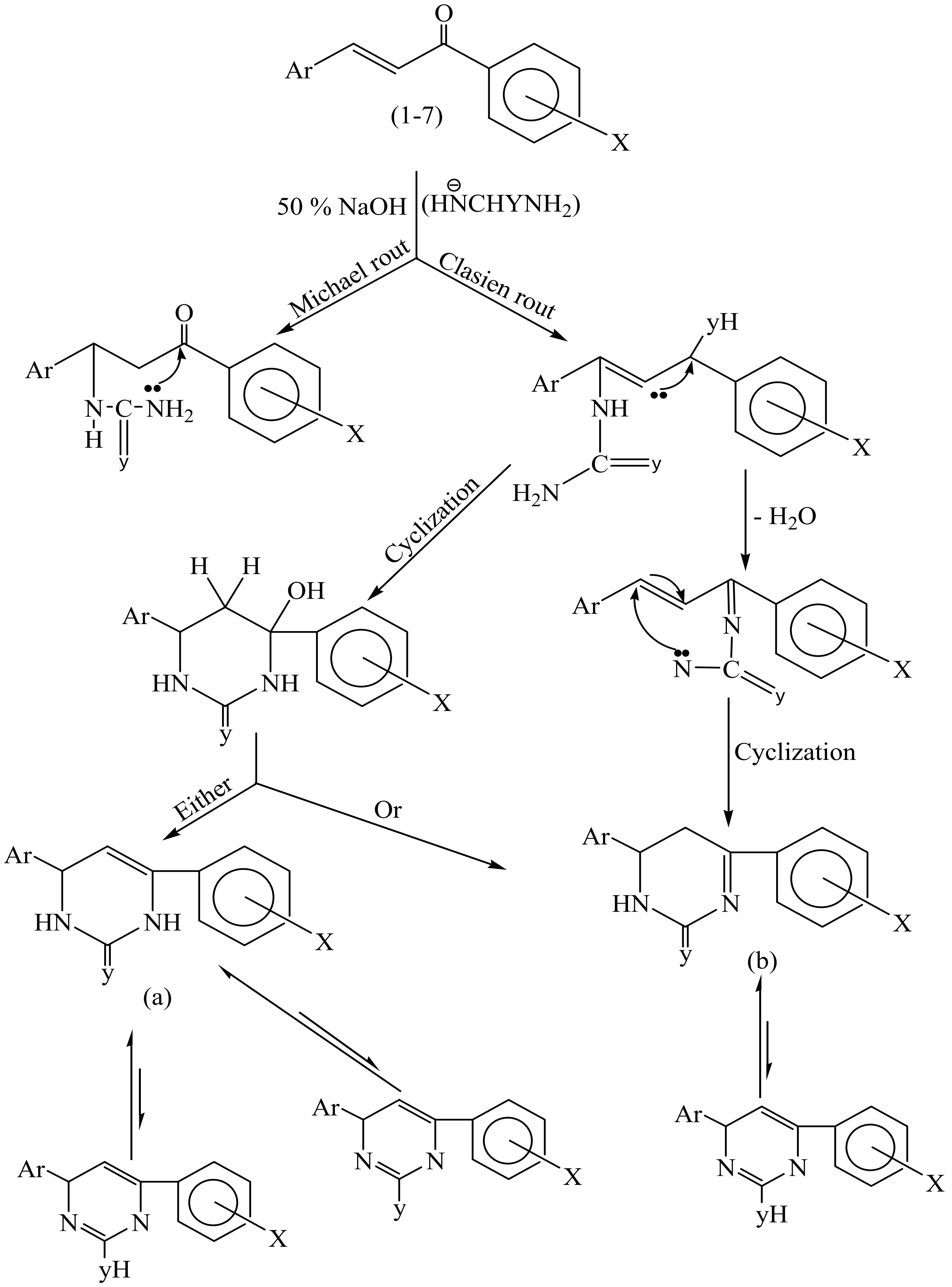
The structure of compounds (8-14) was established by spectroscopic methods (Table 2). The FT, IR spectra showed a strong absorption bands at (1686-1672 cm^{-1}) for the C=O bond stretching and a bands at (1635-1625cm^{-1}) for the C=C bond stretching in addition to broad bands at (3450-3400 cm^{-1}) for the N-H bond stretching.

The U.V spectra of compounds (8-14) (Jackman, 1978) showed λ_{max} at 320-380 nm, i.e, they showed a blue shift relative to the λ_{max} exhibited by chalcones. This blue shift attributed to the destruction of the conjugation.

On the other hand, the condensation of compounds (1-7) with thiourea under phase transfer catalysis afforded the pyrimidine-2-thione compounds (15-21). The structure of these compounds was established on the bases of spectroscopic methods (Table 3).

The FTIR spectra (Williams,1973) showed three characteristic bands at (1167-1160), (1657-1645) and (3450-3400) cm^{-1} attributed to C=S, C=C and N-H (broad) bond stretching respectively. The U.V spectra (Jackman,1978) showed absorption bands at shorter wavelength (blue shift) at 310-420 nm relative to the chalcones (λ_{max} = 380-430 nm). The suggested mechanism for the reaction of chalcones with thiourea is illustrated in Scheme (2).

According to the theoretical calculations the preferred mechanistic route is the Michael addition (H.F and S.E for compound 15a are -25.089 and 24.232 Kcal/mole respectively). This product is more stable than 15b (formed via Claisen addition H.F and S.E are -19.716 and 29.158 Kcal/mole respectively).



y = O, S

Scheme 2: Reaction of chalcone (1-7) with urea and thiourea.

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