Synthesis of New Antipyrines

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Abstract

Synthesis of 4-(amino acetyl acetate) antipyrine has been obtained through the reaction of 4-amino antipyrine with ethyl bromo acetate, then converted to hydrazide derivatives by using hydrazine hydrate. This hydrazide on treatment with various aldehydes and ketones offered Schiff base derivatives. Oxadiazole derivatives have been also synthesized by treatment of above acid hydrazide with CS_2/KOH or p-chlorobenzoic acid in the presence of $POCl_3$.

The synthesized compounds were verified by their IR, UV spectra and C.H.N. analysis data.

الخلاصة

في هذا البحث تم تحضير 4-(امينو استيل اسيتات) انتي بايرين من خلال تفاعل 4-امينو انتي بايرين مع برومو خلات الاثيل وبعدها حولت إلى مشتق الهيدرازايد باستخدام الهيدرازين. وعند مفاعلة هذا الهيدرازايد مع الديهايدات او كيتونات مختلفة أعطت قواعد شيف متنوعة، أيضاً تم الحصول على مشتقات الاوكسادايازول عن طريق تفاعل الهيدرازايد مع CS_2 بوجود KOH أو حامض بارا كلورو البنزويك بوجود $POCl_3$.

شخصت المركبات المحضرة باستخدام بعض الطرق الطيفية (UV, IR) والتحليل الدقيق للعناصر.

Introduction

4-Amino antipyrine derivatives are interesting series of heterocyclic compounds, which have been shown to be diverse biological properties such as anti inflammatory (1), analgesic (2,3,4), bactericidal (5,6), antifungal (7,8).
Moreover, they have been used as analytical reagents for the determination of many enzyme activities (9,10).

This paper reports the synthesis of some new 4-amino antipyrine compounds (esters and its corresponding hydrazide, Schiff bases and oxadiazole derivatives).

Experimental

Melting points were determined on Gallen-Kamp MFB-600 melting point apparatus. IR spectra were recorded on a Pye-Unicam SP3-100 as KBr discs and films. The UV spectra were performed on a Hitachi/UV-2000 spectrophotometer. Elemental analysis of compounds carried out on C.H.N. analyzer type 1160 (Carlo-Erba).

Preparation of 4-(amino ethyl acetate) antipyrine (1) (10): -

A mixture of 4-mino antipyrine (0.15 mole), chloro ethyl acetate (0.15 mole) and sodium carbonate (0.15 mole) in (150 ml) absolute ethanol was refluxed for (2 hrs). After that the mixture was filtered and the filtrate was evaporated under vacuum to give an oily product. This product was purified using column chromatography (silica gel) using chloroform as solvent, (Tables 1,4,7,1).

Preparation of 4-(amino acetic acid hydrazinyl) antipyrine (2) (11): -

A mixture of compound (1) (0.08 mole) and hydrazine hydrate (99%) (0.4 mole) in absolute ethanol was refluxed for (4 hrs). After cooling, the formed precipitate was filtered off and recrystallized from ethanol (Tables 1,4,7,8).

Preparation of Schiff's bases (3-10) (12): -

Compound (2) (0.01 mole) was dissolved in (50 ml) of absolute ethanol. Appropriate aldehyde or ketone (0.02 mole) in (25 ml) of absolute ethanol was added gradually to the mixture that has been refluxed for (2 hrs) and cooled. The product was precipitated, filtered off and recrystallized from appropriate solvent (Tables 2,5,7,8).

Preparation of 4-[aminomethyl-1,3,4-oxadiazole-5-yl-2(4'-chloro phenyl)] antipyrine (11): -

Compound (2) (0.01 mole) was mixed with p-chloro benzoic acid (0.01 mole), the $POCl_3$ (7 ml) was added and the mixture was refluxed for (4 hrs). After that, the reaction mixture poured into crushed ice (100 gm) and made weak basic medium by addition of sodium bicarbonate. The precipitate was filtered, washed with cold water and recrystallized from ethanol (Tables 3,6,7,8).

Preparation of 4-(amino methyl-1,3,4-oxadiazole-5-yl-2-thiol)antipyrine(12): -

Compound (2) (0.005 mole) was dissolved in ethanolic solution (70 ml) of potassium hydroxide (0.005 mole). Carbon disulfide (0.1 mole) was added gradually to the mixture that has been refluxed for (16 hrs). The solvents were evaporated under vacuum, then the residue was poured into crushed ice (30 gm), acidified with dilute hydrochloric acid and left in ice-bath for (60 min). The precipitate was filtered and recrystallized from acetone-hexane (Tables 3,6,7,8).

Results and Discussion

Scheme (1) summarizes all the performed reactions in this work. Physical properties and spectral data of the synthesized compounds were given in tables (1-8).

4-(amino ethyl acetate) antipyrine (1) have been prepared by the reaction of 4-amino antipyrine with ethyl chloro acetate in the presence of Na_2CO_3 through nucleophilic displacement mechanism. The reaction is followed by disappearance of absorption band for NH_2 and appearance of new absorption band at 3320 and 1750 cm^{-1} belonging to the υNH and υCO respectively. UV spectrum of compound (2) showed two intense maxima at 339 nm and 261 nm due to ($n \longrightarrow \pi^*$) and ($\pi \longrightarrow \pi^*$) electronic transitions respectively.

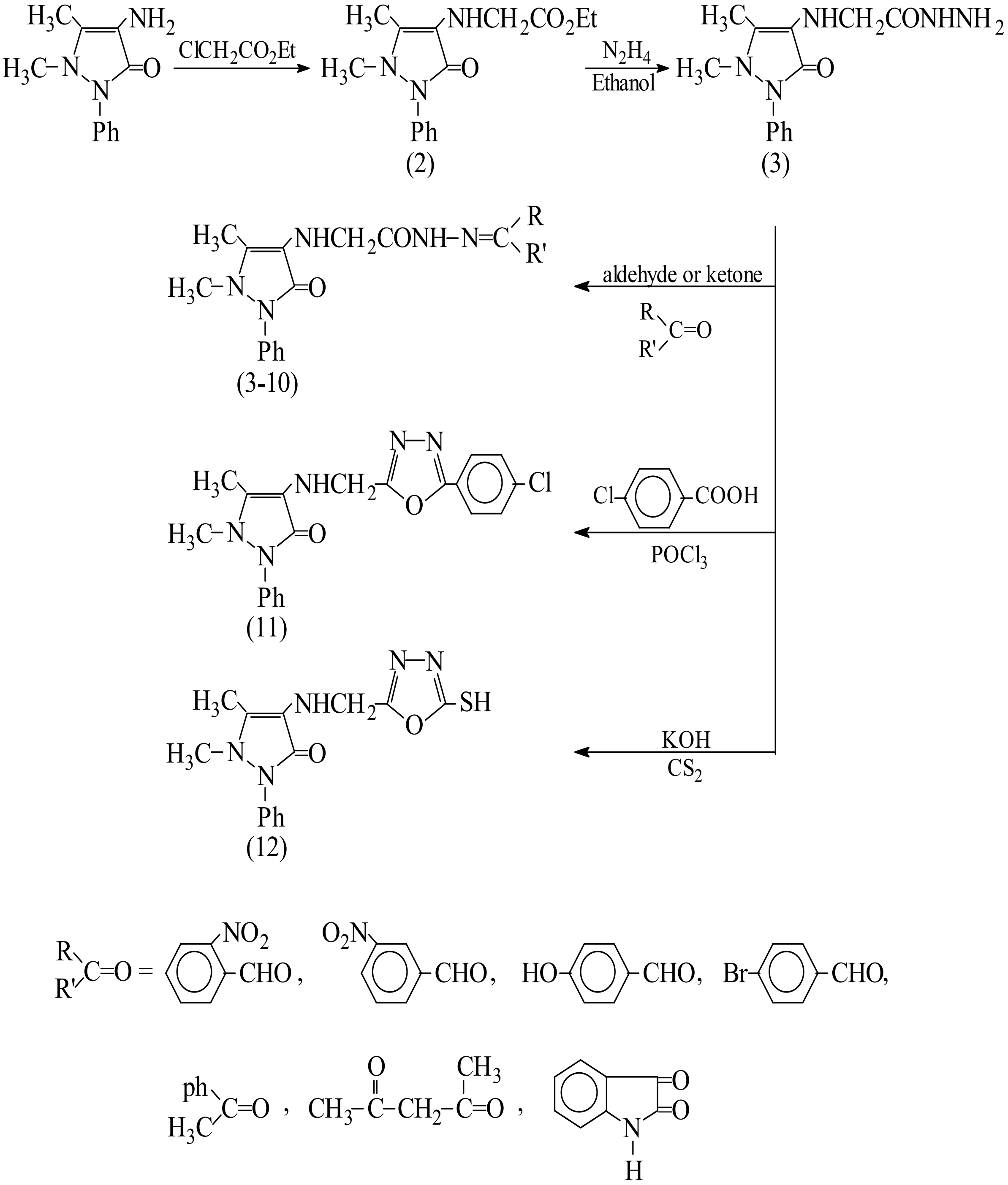
The treatment of ester (1) with hydrazine hydrate led to the formation of acid hydrazide derivatives (2). The reaction was proceeded by nucleophilic substitution (tetrahedral mechanism) of hydrazine to the ester carbonyl group giving the corresponding hydrazide (2). This hydrazide (2) have been identified by its elemental analysis and some spectral data, the IR spectrum of it showed the appearance of characteristic absorption bands near 3380-3480 cm^{-1} due the NH_2 and υNH, and 1670 cm^{-1} which belonged to the amide carbonyl group υC=O. Condensation of this acid hydrazide (2) with various aldehydes and ketones yielded the corresponding hydrazones (3-10).

These Schiff bases exhibited the bands 3280-3300 cm^{-1} (NH), 1650-1680 cm^{-1} (CONH) and 1580-1630 cm^{-1} (C=N).

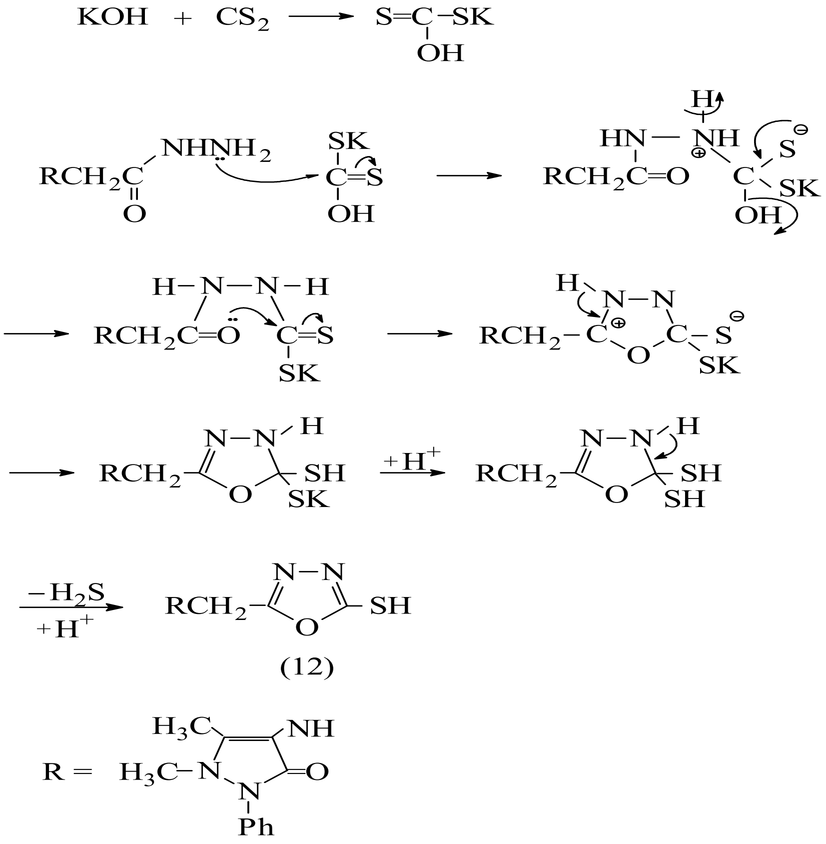
Refluxing the p-chloro benzoic acid with equimolecular amount of acid hydrazide (2) in the presence of phosphorous oxy chloride for (4 hrs) offered good yield of the corresponding 4-oxadiazole derivative (11). The IR spectrum of the oxadiazole (11) displayed peacks at 3150, 1660, 1630 and 1180 cm^{-1} for NH, C=O, C=N and C-O-C functions respectively.

Finally, refluxing the acid hydrazide (2) with equimolar amount of ethanolic KOH and excess of carbon disulfide for 16 hrs yielded the corresponding mercapto-1,3,4-oxadiazole derivative (12). The reaction was followed by thin layer chromatography using $CHCl3$:hexane (1:4) as a solvent system. However, the long time reaction might be attributed to the steric effect. The IR spectrum of it showed the appearance of characteristic absorption bands near 3150, 1660, 1620, 1200 and 1140 cm^{-1} due to the NH, C=O, C=N, C=S and C-O-C functions respectively.

It was believed that the oxadiazole derivative (12) formed by internucleophilic attack of hydrazino group, followed by the loss of hydrogen sulphide molecule as shown in scheme (2).

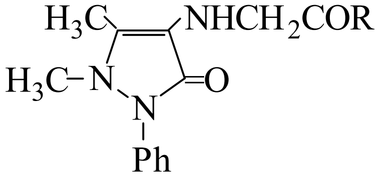

ClCH₂CO₂Et
N₂H₄
Ethanol
(2)
(3)
aldehyde or ketone
(3-10)
POCl₃
(11)
KOH
CS₂
(12)

Scheme 1



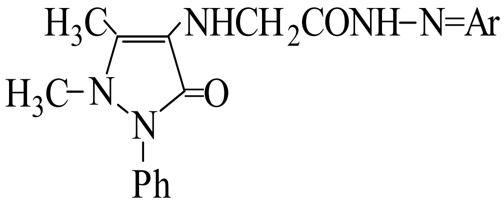
Scheme 2

Table (1): Physical properties of compounds (1, 2)



Comp. No.	-R	M.P. (°C)	Yield (%)	Purification solvent	Molecular formula
1	$-OC_2H_5$	Oily	82	Chloroform	$C_{15}H_{19}N_3O_3$
2	$-NHNH_2$	Oily	77	Ethanol	$C_{13}H_{15}N_5O_2$

Table (2): Physical properties of Schiff bases (3-10)



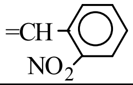
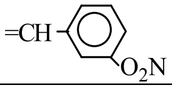
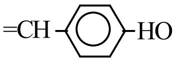
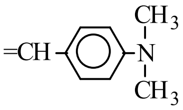
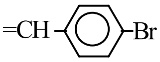
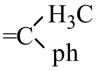
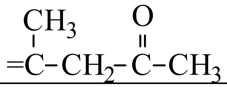
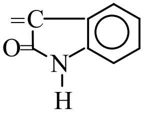
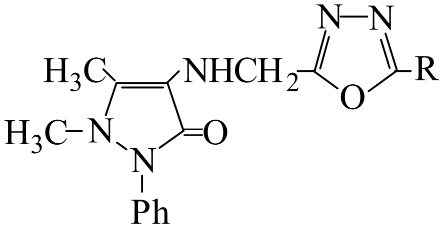
Comp. No.	=Ar	M.P. (°C)	Yield (%)	Purification solvent	Molecular formula
3		207-209	86	Acetone	$C_{20}H_{20}N_6O_4$
4		192-194	77	Acetone-Hexane	$C_{20}H_{20}N_6O_4$
5		120-122	78	Ethanol-Hexane	$C_{20}H_{21}N_5O_3$
6		255-257	70	Ethanol-Hexane	$C_{21}H_{26}N_6O_2$
7		216-218	61	Acetone	$C_{20}H_{20}N_5O_2Br$
8		110-112	93	Acetone-Hexane	$C_{21}H_{23}N_5O_2$
9	 $=\overset{CH_3}{\overset{\mid}{C}}-CH_2-\overset{O}{\overset{\parallel}{C}}-CH_3$	105-107	56	Chloroform	$C_{18}H_{23}N_5O_3$
10		190-192	63	Acetone-Hexane	$C_{21}H_{20}N_6O_3$

Table (3): Physical properties of compounds (11,12)



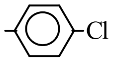
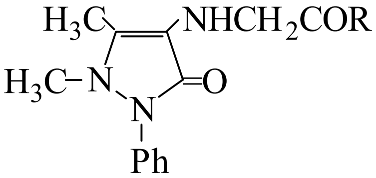
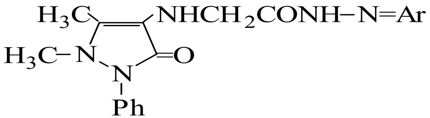
Comp. No.	-R	M.P. (°C)	Yield (%)	Purification solvent	Molecular formula
11		225-227	75	Ethanol	$C_{20}H_{18}N_5O_2Cl$
12	-SH	170-172	76	Acetone-Hexane	$C_{14}H_{15}N_5O_2S$

Table (4): IR Spectral data of compounds (1,2)



Comp. No.	-R	υ(C-H) (cm^{-1}) aromatic	υ(C-H) (cm^{-1}) aliphatic	υ(N-H) (cm^{-1})	υ(C=O) (cm^{-1})	υ(C=C) (cm^{-1}) aromatic	Others (cm^{-1})
1	$-OC_2H_5$	3010	2930	3320	1750	1600	-
2	$-NHNH_2$	3020	2960	3380	1670	1610	υNH_2 3480

Table (5): IR Spectral data of compounds (3-10)



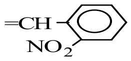
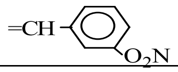
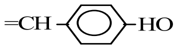
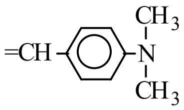
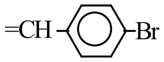
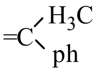
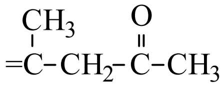
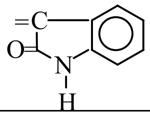
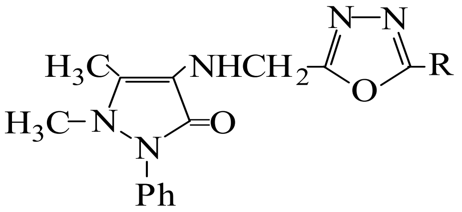
Comp. No.	=Ar	υ(C-H) (cm^{-1}) aromatic	υ(C-H) (cm^{-1}) aliphatic	υ(N-H) (cm^{-1})	υ(C=O) (cm^{-1})	υ(C=N) (cm^{-1}) aromatic	Others (cm^{-1})
3		3050	2960	3300	1660	1580	υC-NO_2 1540
4		3080	-	3280	1650	1600	υC-NO_2 1500
5		3100	2960	3300	1660	1600	υC-OH 3410
6		3050	2940	3290	1680	1600	-
7		3040	2650	3300	1660	1620	-
8	 $=C(H_3C)(ph)$	3000	2920	3300	1665	1600	-
9	 $=C(CH_3)-CH_2-C(=O)-CH_3$	3050	2980	3305	1670	1630	υC=O 1700
10		3000	2920	3310	1680	1600	υC=O 1710

Table (6): IR Spectral data of compounds (11-12)



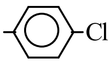
Comp. No.	-R	υ(C-H) (cm^{-1}) aromatic	υ(C-H) (cm^{-1}) aliphatic	υ(N-H) (cm^{-1})	υ(C=O) (cm^{-1})	υ(C=C) (cm^{-1}) aromatic	Others (cm^{-1})
11		3000	2840	3150	1660	1630	υC-O 1180 υC-Cl 750
12	-SH	3000	2920	3150	1660	1620	υC=S 1200 υC-O 1140

Table (7): UV Spectral data of some synthesized compounds

Comp. No.	λ_{max} EtOH (95%)
1	435, 261, 311.5, 339
2	270.5, 249, 318
6	442.5, 249, 272, 319.5
7	319.5, 249, 271, 386
8	306.5, 255.5, 338.5
10	414.5, 248.5, 269.5, 322
11	248.5, 270, 323.5
12	248.5, 268.5, 294.5, 351.5

Table (8): C.H.N analysis of some synthesized compounds

Comp. No.	C.H.N analysis % calculated (found %)		
	C %	H %	N %
1	62.22 (61.62)	6.56 (6.94)	14.52 (14.33)
2	56.67 (56.28)	5.44 (5.60)	25.43 (25.22)
3	85.93 (85.63)	4.91 (5.08)	17.18 (17.02)
5	63.45 (63.19)	5.55 (5.71)	18.45 (18.29)
8	62.33 (61.95)	5.68 (5.81)	17.31 (17.13)
10	62.33 (60.41)	4.94 (5.09)	20.77 (20.49)
11	60.79 (60.41)	4.55 (4.72)	17.75 (17.56)
12	52.95 (52.85)	4.72 (4.84)	22.06 (21.88)

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