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Synthesis of Barbiturate Derivatives from Imines

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Abstract

Barbiturates were prepared involving the reaction of aromatic Schiff bases with benzoyl chloride to give N-[α-chloro-α-dimethylaminobezyl]-N-aryl-benzanilide. The reaction of the latter with diethylmalonate in basic media to give N-[α-diethylmalonyl-α-p-dimethylaminobenzyl]-N-aryl-benzanilide. The latter condense with urea in basic media afforded derivatives of barbiturate which known to act as hypnotics.

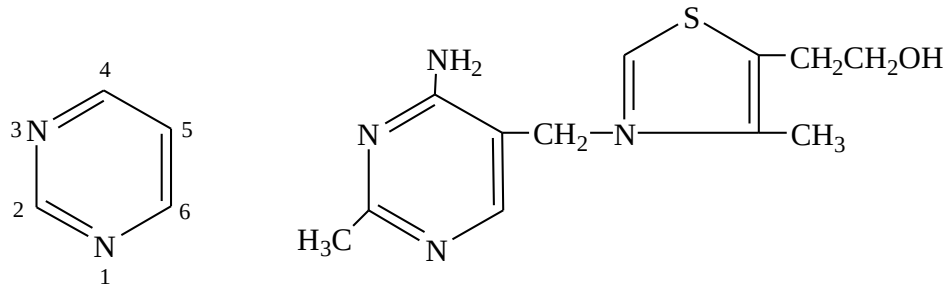
Introduction

In recent years there has been an increased interest in the chemistry of heterocyclic molecules because of their biological significance[(1)]. Schiff bases can be used in industrial chemistry and inorganic chemistry field[(2,3)]. There are many methods found in the literatures to prepare Schiff bases, specially through the condensation of aldehydes or ketenes with primary amines[(4)]. Also reduction of nitriles compounds were carried out either by lithium Aluminum Hydride ($LiALH_4$) or addition of Grignard reagent afforded the imines[(5,6)].

In this paper we reported a new method to synthesis of barbiturate derivatives from the aromatic Schiff bases.

Barbiturates are compounds contain a pyrimidine ring[(7)]. Pyrimidine is a six-membered ring with two nitrogen atoms. The chemistry of pyrimidine compounds and its biochemistry are very important especially in the biosynthesis of lipids derivatives and complex carbohydrates[(8)]. Pyrimidines are constituent of an important products like drags that are used as anti bacterial and malaria[(9)], B_1 and B_2 vitamins[(9)], coffee

and tea in their caffeine's[10]. Medically the barbiturates which are important pyramiding derivatives are used as hypnotics[11].



Pyrimidine B_1 vitamin (Thiamine)

Experimental

Melting points (M.P.)were measured by: Stuart Melting point Apparatus and were uncorrected. Infrared spectra (FT.IR) were recorded as (KBr) discs by: Shimadzu 8400 FTIR Spectrophotometer in the range (4000-450) cm^{-1}. Ultra violet-visible spectra were recorded in the region (900-200) nm for 10^{-3}m solution in (EtOH) at 25C° by: Shimadzu 160 spectrophotometer.

Synthesis of Schiff bases[12]

A mixture of equimolar amounts (0.015mole) of aromatic aldehydes and primary amine was dissolved in (20ml) of absolute ethanol containing a drop of glacial acetic acid and refluxed for (2hrs). the reaction mixture was allowed to cool to room temperature then filtered. Re-crystallization from ethanol gave a colored crystals of: N-benzylideneareneamines [1-4].

Synthesis of N-α-chlorobenzyl-N-aryl-benzailide[13]

Acetyl chloride solution (0.01mole) in (10ml) absolute benzene was added dropwise to the solution (0.01mole) benzylideneareneamine dissolved in (25ml) absolute benzene. The reaction mixture was refluxed for (2hrs.) with stirring. The solution was normally allowed to cool at room temperature, and the precipitated crystals were filtered and re-crystallized from ethanol to yield colored crystals of: N-α-chlorobenzyl-N-aryl-benzailides[5-8].

Synthesis of N-[α-diethylmalonyl-α-p-dimethylaminobenzyl]-N-aryl-benzanilide

A mixture of (0.01mole) of diethyl malonate and (10ml) of ethanolic solution of sodium ethoxide was added to a solution of (0.01mole) of N-[α-chloro-α-p-dimethylaminobenzyl]-N-aryl-benzanilide in (20ml) of absolute ethanol. The reaction

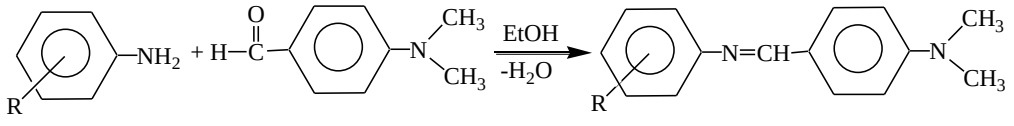
mixture was refluxed for (4hrs.) with stirring. The solvent was evaporated. The resulting was allowed to cool to room temperature, and the participated crystals was filtered, washed with 2% Na_2CO_3 solution, then re-crystallized from ethanol to give: N-[α-diethylmalonyl-α-p-dimethylaminobenzyl]-N-aryl-benzanilide[9-12].

Synthesis of α-[N-benzyl-N-aryl]amino-α-p-dimethylaminobenzyl-barbituric acid

A solution of (0.005mole) of urea in (15mL) of dry acetone was added to a solution of (0.005mole) of N-[α-diethylmalonyl-α-p-dimethylaminobenzyl]-N-aryl-benzanilide in (15mL) of dry acetone. The reaction mixture was refluxed for (7hrs.) with stirring. The solvent was evaporated and the remaining crystals was filtered, re-crystillized from ethanol to yield: α-[N-benzyl-N-aryl]amina-α-p-dimethylaminobenzyl-barbituric acids[13-16].

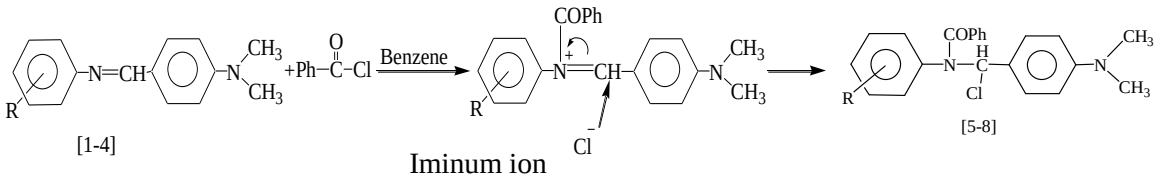
Result and Discution

Aromatic Schiff bases are good starting material to prepare heterocyclic compounds[12]. Aromatic Schiff bases were prepared by acid-catalyzed reaction of aromatic aldehydes with aromatic amines in boiling absolute ethanol[12].



Where R=o-NO_2, m-NO_2, p-NO_2, 2-NO_2-4-Cl

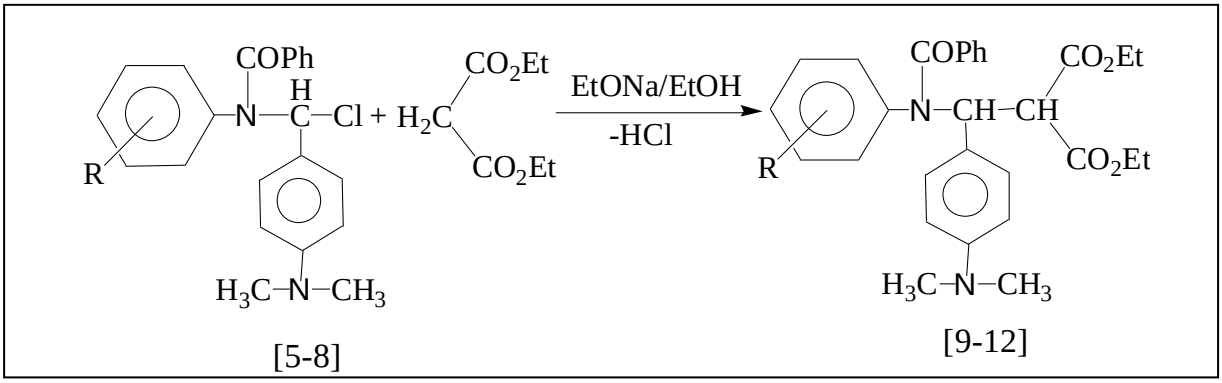
Schiff bases are react with benzoyl chloride to yield N-α-chlorobenzyl-benzanilide [5-8] in good yield[13].



The nitrogen atom attacks the carbon atom of the carbonyl group displacing the chloride ion to from iminium ion. Chloride ion attacks the iminium carbon yields benzanilide derivatires [5-8]. The IR spectra of compounds [5-8] showed an absorption band at (1640-1665)cm^{-1} due to (C=O) of $\left(\begin{matrix}O\\ \|\\ N—C\end{matrix}\right)$ group, appearance of aliphatic (C-Cl) absorption band at (825-830)cm^{-1}[14].

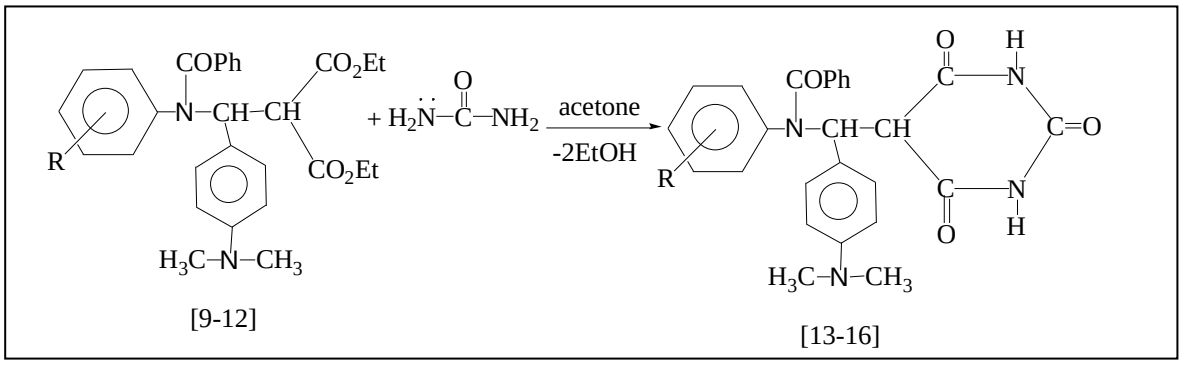
The U.V spectra of compounds [5-8] showed absorption maxima at (305-343)nm due to charge transferee.

N-[α-chloro-α-dimethylaminobenzyl]-N-aryl-benzanilides undergo nucleophilic substitution reaction when treated with diethyl malonate in basic medium to give N-[α-P-diethylmalonyl-α-p-dimethylaminobenzyl]-N-aryl-benzanilides [9-12] with elimination of HCl.



The IR of compounds [9-12] gave an absorption band about (1755-1735)cm^{-1} due to C=O of ester, and around (1685-1670)cm^{-1} due to C=O of amide, and disappearance of aliphatic (C-Cl) band at (830-825)Cm^{-1}.[14]

The U.V spectra showed absorption maxima at (358-219)nm. N-[α-diethylmalonyl-α-p-dimethylaminobenzyl]-N-aryl-benzanilides [9-12] are condensed with urea by nucleophilic substitution to give the pyrimidine derivatives (barbiturates) [13-16].



The IR for barbiturate derivatives gave an absorption band at (3280-3260)cm^{-1}due to(N-H), and at (1690-1680)cm^{-1}due to $\left(-NH-\overset{O}{\overset{\|}{C}}-\right)$.[14]

The U.V spectra of barbiturate derivatives showed absorption maxima at (380-210)nm.

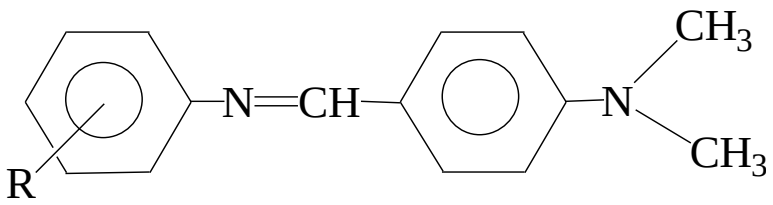


Table (I): Physical and spectroscopic data of imines[1-4]

Comp.	R	Molecular formula	m.p.C°	Yield %	F.T.I.R. Cm^{-1}(KBr)						U.V. λ_{max}nm (EtOH)
					$\upsilon_{C=N}$	$\upsilon_{C=H}$ aliphatic	$\upsilon_{C=H}$ aliphatic	$\upsilon_{C=N}$	$\upsilon_{C=NO2}$	$\upsilon_{C=Cl}$	
1	o-NO_2	$C_{15}H_{15}O_2N_3$	103-105	58	1603	3050	2845	1245	1519&1342	-	243
2	m-NO_2	$C_{15}H_{15}O_2N_3$	148-150	61	1598	3045	2843	1240	1504&1334	-	242
3	p-NO_2	$C_{15}H_{15}O_2N_3$	198-200	69	1598	3050	2845	1243	1504&1373	-	248
4	2-NO_2,4-Cl	$C_{15}H_{14}O_2N_3Cl$	222-224	51	1604	3055	2850	1245	1520&1340	817	238

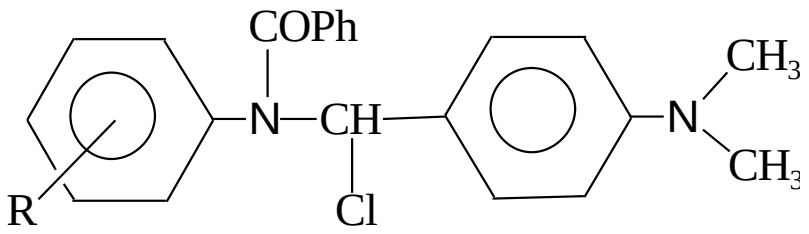


Table (II): Physical and spectroscopic data of N-[α-chloro-α-dimethylaminobezyl]-N-aryl-benzanilide.[5-8]

Comp.	R	Molecular formula	m.p.C°	Yield %	F.T.I.R. Cm^{-1}(KBr)						U.V. λ_{max}nm (EtOH)
					$\upsilon_{C=N}$	$\upsilon_{C=H}$ aliphatic	$\upsilon_{C=H}$ aliphatic	$\upsilon_{C=N}$	$\upsilon_{C=NO2}$	$\upsilon_{C=Cl}$	
5	o-NO_2	$C_{22}H_{20}O_3N_3Cl$	171-173	62	1640	3060	2860	1245	1545&1330	830	305
6	m-NO_2	$C_{22}H_{20}O_3N_3Cl$	197-199	80	1660	3050	2850	1240	1540&1345	825	336
7	p-NO_2	$C_{22}H_{20}O_3N_3Cl$	210-212	83	1650	3050	2855	1240	1540&1343	825	305
8	2-NO_2,4-Cl	$C_{22}H_{19}O_3N_3Cl_2$	257-260	65	1665	3063	2865	1245	1540&1350	830	343

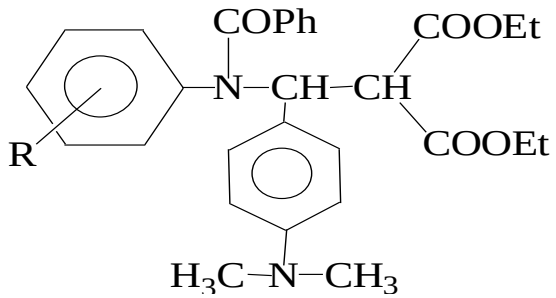


Table (III): Physical and spectroscopic data of N-[α-diethylmalonyl-α-p-dimethylaminobenzyl]-N-aryl-benzanilide[13-16].

Comp.	R	Molecular formula	m.p.C°	Yield %	F.T.I.R. Cm^{-1}(KBr)								U.V. λ_{max}nm (EtOH)
					$\upsilon_{C=O}$ amide	$\upsilon_{C=O}$ ester	$\upsilon_{C=H}$ aliphatic	$\upsilon_{C=H}$ aliphatic	$\upsilon_{C=N}$	υ_{C-O-C}	$\upsilon_{C=NO2}$	$\upsilon_{C=Cl}$	
9	o-NO_2	$C_{29}H_{31}O_7N_3$	225-227	57	1670	1750	3055	2850	1240	1240 1130	1540&1345	-	343 238
10	m-NO_2	$C_{29}H_{31}O_7N_3$	239-241	70	1670	1745	3045	2850	1240	1240 1130	1535&1340	-	345 219
11	p-NO_2	$C_{29}H_{31}O_7N_3$	252-254	68	1675	1750	3045	2850	1240	1240 1130	1540&1340	-	358 240
12	2-NO_2,4-Cl	$C_{29}H_{30}ON_3Cl$	280-283	46	1685	1755	3058	2850	1245	1245 1136	1545&1335	830	344 239

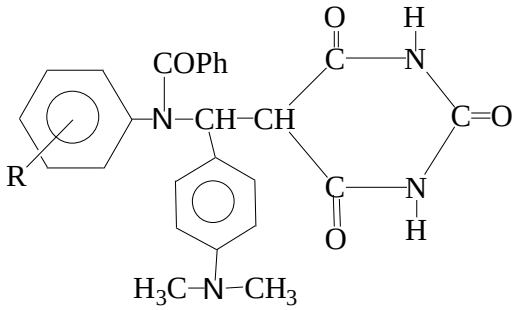


Table (IV): Physical and spectroscopic data of α-[N-benznzyl-N-aryl]amina-α-p-dimethylaminobenzyl-barbituric acid[13-16]

Comp.	R	Molecular formula	m.p.C°	Yield %	F.T.I.R. Cm^{-1}(KBr)								U.V. λ_{max}nm (EtOH)
					υ_{N-H}	$\upsilon_{C=O}$ lactam	$\upsilon_{C=O}$ amide3°	$\upsilon_{C=H}$ aliphatic	$\upsilon_{C=H}$ aliphatic	$\upsilon_{C=N}$	$\upsilon_{C=NO2}$	$\upsilon_{C=Cl}$	
13	o-NO_2	$C_{26}H_{23}O_6N_5$	257-259	45	3275	1685	1665	3050	2855	1245	1545&1335	-	344 210
14	m-NO_2	$C_{26}H_{23}O_6N_5$	269-270	56	3260	1580	1660	3045	2850	1240	1540&1340	-	380 245
15	p-NO_2	$C_{26}H_{23}O_6N_5$	279-281	49	3270	1685	1670	3045	2855	1240	1540&1340	-	304 247
16	2-NO_2,4-Cl	$C_{26}H_{22}O_6N_5Cl$	295-298	43	3280	1690	1680	3048	2860	1240	1545&1330	830	300 247

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تحضير مشتقات الباربيتيورات من الايمينات .

أحلام جاسم زاير

قسم الكيمياء ، كلية التربية – أبن الهيثم ، جامعة بغداد ، الاعظمية ، العراق

الخلاصة

تحضر الباربيتيورات من تفاعل قواعد شيف الاروماتية مع كلوريد البنزويل ليعطي N - [α - كلوريد - α – ثنائي مثيل أمينو بنزويل] - N - آريـل - بنزانيليـــد . تتفاعل الاخيرة مع ثنائي أثيل مالونيت في وسط قاعدي لتعطـــي N - [α - ثنائي أثيل مالونيل - α - بارا - ثنائي مثيل أمينو بنزيل] - N -آريـل - بنزانيليـــد . تتكاثف الاخيرة مع يوريا في وسط قاعدي لتعطي مشتقات الباربيتيورات التـــي تستعمل كـ " منومات " .