Synthesis of Some Substituted Benz/acetamidines

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الملخص

تم في هذا البحث تحضير عدد من معوضات اسيتاميدين من خلال معاملة انهدريد الفثاليك مع حامض بارا-امينو بنزويك او مع الكلايسين ليعطي الحامض المقابل الذي تم تحويله الى كلوريد الحامض باستخدام كلوريد الثايونيل. تم مفاعلة كلوريد الحامض مع ثنائي اثيل امين او ثنائي بيوتيل امين ليعطي الاميدات. حولت الاميدات الى النواتج النهائية من خلال مفاعلتها مع الانيلين او مشتقاته بوجود $POCl_3$.

شخصت المركبات المحضرة باستخدام طيف الاشعة تحت الحمراء وطيف الاشعة فوق البنفسجية والطرق الفيزياوية.

ABSTRACT

In the present work the synthesis of substituted acetamidines was achieved. Phthalic anhydride was treated with p-aminobenzoic acid or glycine to give the corresponding acid which then converted to acid chloride with thionyl chloride. The acid chloride was treated with diethyl amine or dibutyl amine to give amides. The amides then converted to final products by their reaction with aniline or its substituents and $POCl_3$.

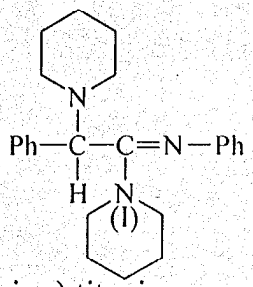
The structure of the synthesized compounds was confirmed by IR, UV and physical means.

INTRODUCTION

The synthesis of substituted imidines was studied in recent years as a program to develop new anticoagulants for the treatment of throm-botic disorcless.

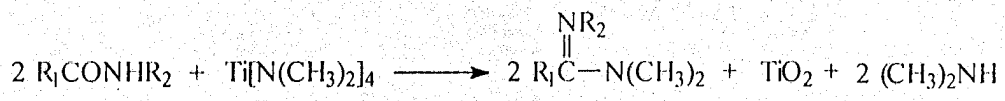
2-Hydroxy benzamidines have been prepared from 3-amino benzisoxazoles by reductive cleavage of nitrogen-oxygen bond using catalytic hydrogenation[1]. Phosgene was also reacted with 2 moles of acetanilide to give N,N`-diphenyl acetamidine[2].

The aminolysis of gem-dichloroaziridine provides a convenient synthesis of amidines as compound[3] (I).



(I)

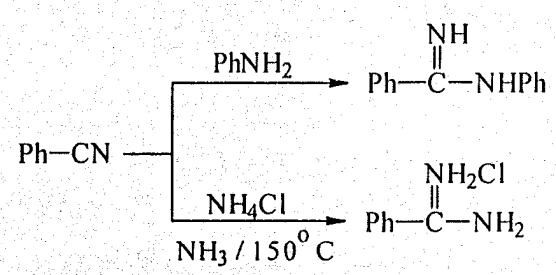
Tetrakis (dimethyl amino) titanium reacts with N-mono substituted carboxamides to give trisubstituted amidines as in the following equation[4].



$2\ R_1CONHR_2 + Ti[N(CH_3)_2]_4 \longrightarrow 2\ R_1C(=NR_2)-N(CH_3)_2 + TiO_2 + 2\ (CH_3)_2NH$

$R_1 = CH_3, C_6H_5$
$R_2 = CH_3$

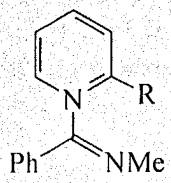
Amidines was prepared from nitriles by their reaction with amines or ammonium salts as in the following equations[5].



$Ph-CN \xrightarrow{PhNH_2} Ph-C(=NH)-NHPh$

$Ph-CN \xrightarrow[NH_3 / 150^{\circ} C]{NH_4Cl} Ph-C(=NH_2Cl)-NH_2$

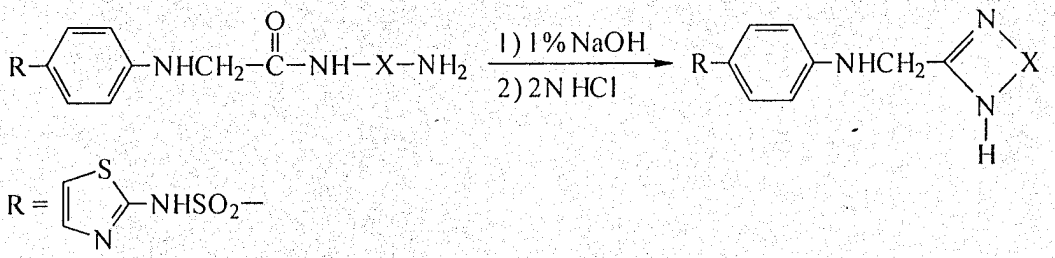
The reaction of N-methyl benzamide with TF_2O_2 in pyridine, then with Grignard reagents at (-78 °C) gave compound (I).



(I)

Compound (I) oxidized with DDQ/THF to give 2-alkyl pyrimidines[6].

Cyclic amidine was also prepared as in the following equation[7].



X = ethylene diamine, 1-phenylene diamine

The treatment of α,β-unsaturated trifluoroketones with amidines in acetonitrile gave the corresponding 4-hydroxy-4-(trifluoromethyl)-3,5,6-trihydropyrimidines, which was dehydrated with phosphorus oxychloride then oxidation with manganese oxide, producing 2,6-disubstituted-4-(trifluoromethyl) pyrimidines[8].

EXPERIMENTAL

Melting points were measured using Electrothermal 9300 and are uncorrected. The IR spectra were recorded on Brucker FT-IR Spectrophotometer, Tensor 27, using KBr discs. The UV spectra were recorded on UV-Visible Shimadzu 1601 Spectrophotometer.

Synthesis of acids (1-2):

A mixture of p-aminobenzoic acid or glycine (0.01 mole) and phthalic anhydride (0.01 mole) was heated with shaking on a sand bath at (195-200 °C) for 10 min and then left at this temperature for 15 min. The product was solidify on cooling. Water (50 ml) was then added and filtered. The product was recrystallized from water to give white powder[9].

Comp. (1)	m.p. 192-194 °C Lit[10] 193-196	Yield 85%
Comp. (2)	m.p. 281-283 Lit[11] 284-286	Yield 87%

Synthesis of acid chlorides (3-4):

The acid (1 or 2) (0.05 mole) was mixed with thionyl chloride (0.05 mole) in a round bottomed flask fitted with condenser and drying tube. The mixture then refluxed for two hours (60-70 °C) with stirring, the excess thionyl chloride was evaporated under reduced pressure to give the products[12].

Comp. (3)	m.p. 83-85 °C	Yield 60%
Comp. (4)	m.p. 248-250 °C	Yield 70%

Synthesis of amides (5-8):

Acid chloride (3 or 4) (0.01 mole) was dissolved in dry THF (15 ml), diethyl amine or dibutyl amine (0.01 mole) was added with stirring. The mixture was refluxed for two hours, cool and then water (30 ml) was added to give solid product, which was recrystallized from ethanol[12].

Synthesis of substituted amidines (9-20):

To amides (5-8) (0.37 mole) in dry benzene (50 ml), phosphorous oxychloride (23 g) was added with stirring, the mixture was allowed to stand at room temperature for 18 hrs. Aniline (11.6 g) was added dropwise keeping the temperature at 35 °C, then stirred for 6 hrs, and the mixture was extracted with benzene, then cold sodium hydroxide solution was added until the aqueous solution is basic. The benzene layer was separated and dried, then evaporated to give the product[5].

RESULTS AND DISCUSSION

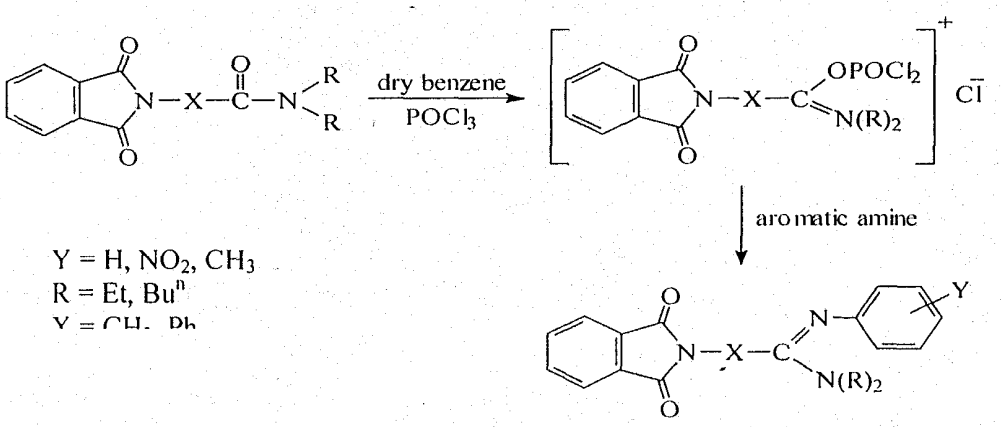
The synthesis of substituted amidines was studied by many research worker and could be prepared using several methods. One of these methods is the condensation of nitriles with amines in presence of Friedal-Craft catalysts such as $AlCl_3$, BF_3, $ZnCl_2$, $FeCl_3$ and $SnCl_4$[5]. Other method was adjusted through substitution reaction which involve the reaction of amines with imidate[14] and imidoyl chloride[15].

In this paper some substituted benz/acetamidines were prepared from phthalic anhydride which was treated with p-aminobenzoic acid or glycine to give the corresponding acids (1 and 2), (Scheme 1), the prepared acids were identified by I.R and UV spectrum ν cm^{-1} (1715-1725) (C=O) and (2935-2985) (O-H), λ_{max} (374-312) nm.

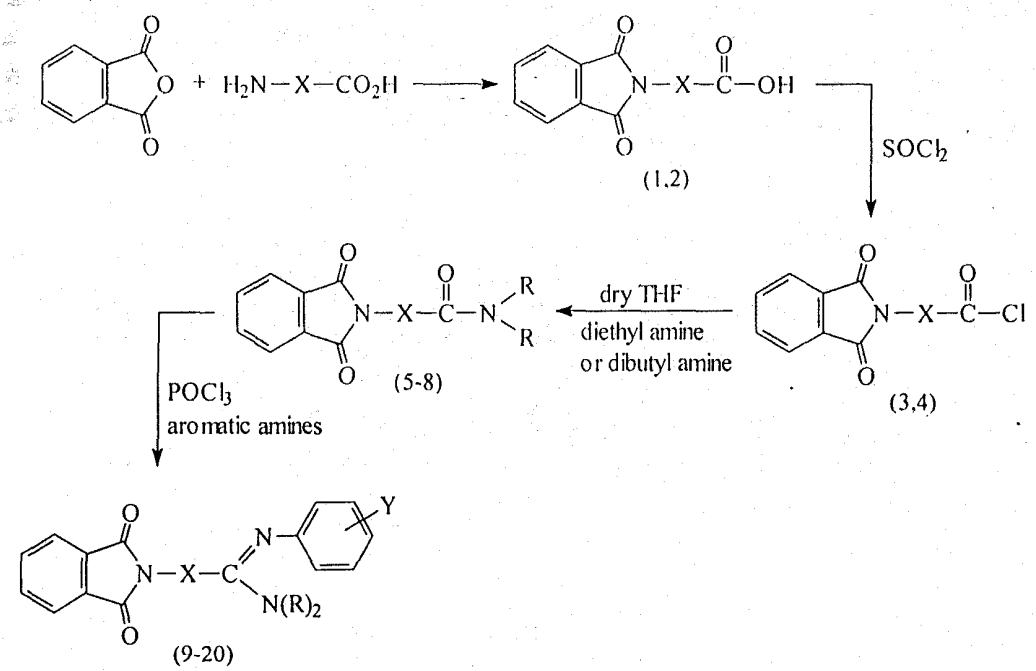
The acids (1,2) were then converted to the corresponding acid chloride (3,4) by their reaction with thionyl chloride. The acid chlorides (3,4) were treated with diethyl amine or dibutyl amine to give amides (5,6) and (7,8) respectively.

The compounds (5-8) show absorptions at ν cm^{-1} (1621-1689) (C=O amide) and (1717-1724) (C=O), λ_{max} (313-305) nm.

Final products were obtained by the reaction of amides with $POCl_3$ then with aniline and substituted aniline as in the following mechanism.



The physical spectral and data are listed in Tables (1) and (2).



9,11,13	$R = C_2H_5$	$X = CH_2$	$Y = NO_2, CH_3, H$
10,12,14	$R = C_2H_5$	$X = C_6H_4$	$Y = NO_2, CH_3, H$
15,17,19	$R = C_4H_9$	$X = CH_2$	$Y = NO_2, CH_3, H$
16,18,20	$R = C_4H_9$	$X = C_6H_4$	$Y = NO_2, CH_3, H$

Scheme (1)

Table (1): Physical and spectral data for compounds (5-8)

Comp. No.	m.p. °C	Yield %	Colour	I.R. (KBr) ν cm^{-1}		UV (EtOH) λ_{max} nm
				C=O amide	C=O	
5	117-119	68	Brown	1660	1723	308
6	137-139	59	Grey	1689	1722	309
7	68-70	42	Brown	1668	1724	313
8	271-273	38	Grey	1621	1717	322

Table (2): Physical and spectral data for compounds (9-20)

Comp. No.	m.p. °C	Yield %	Colour	I.R. (KBr) ν cm^{-1}				UV (EtOH) λ_{max} nm
				C=O	C=N	C-N	NO_2	
9	150-152	73	Yellow	1717	1621	1220	1421	370
10	115-117	85	Yellow	1716	1631	1298	1509	371
11	123-125	47	Dark broun	1717	1661	1221	-	302
12	88-90	72	Brown	1717	1652	1177	-	318
13	205-207	45	Yellow	1710	1671	1220	-	317
14	234-236	50	Light grey	1703	1654	1259	-	307
15	68-70	75	Yellow	1719	1664	1218	1506	377
16	Oily	70	Light brown	1716	1600	1112	1505	308
17	76-78	45	Brown	1719	1664	1218	-	309
18	78-80	67	Light brown	1715	1623	1220	-	304
19	146-148	52	Yellow	1727	1655	1202	-	306
20	237-240	60	Brown	1716	1655	1219	-	324

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