Synthesis and characterization of some new hydrazones and 1, 3, 4 – oxadiazoles derived from phthalyl amino acid

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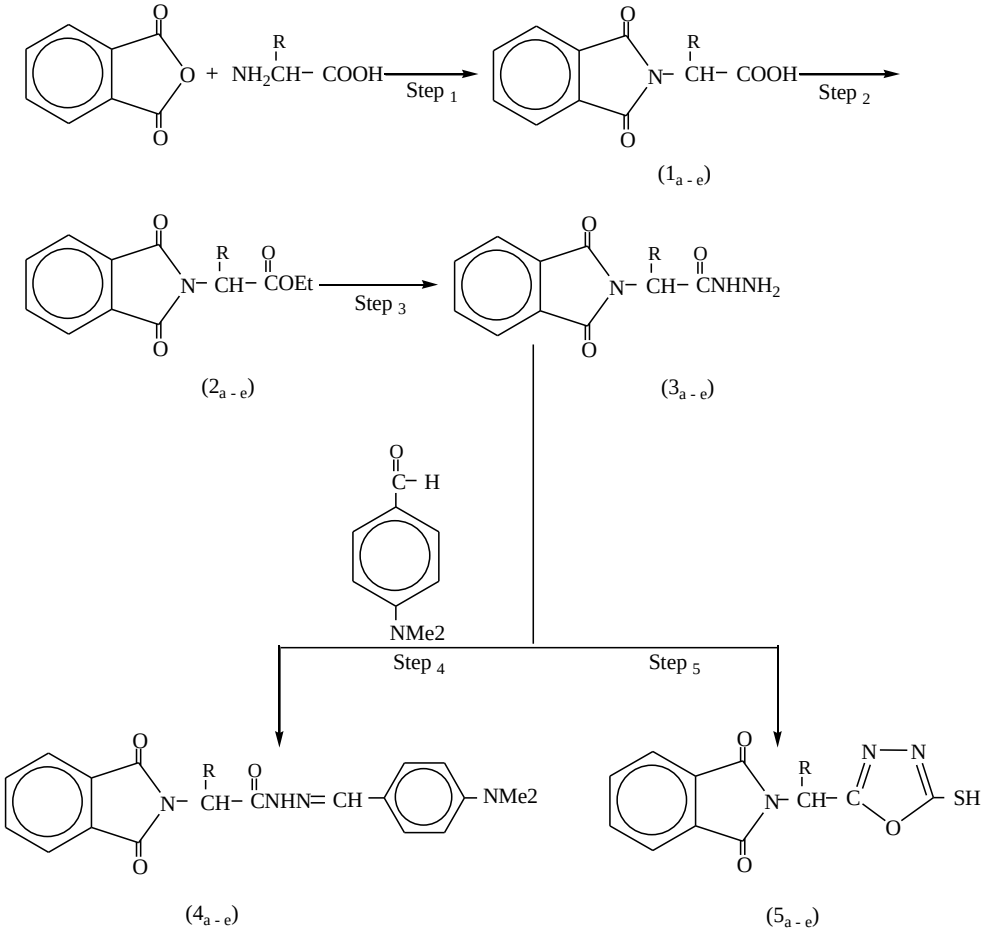
Abstract

The reaction of the available starting material Phthalic anhydride with various amino acids gave Phthalyl amino acids (1_{a-e}). Fischer esterification of compounds (1_{a-e}) afforded the corresponding esters (2_{a-e}) . The synthesized esters (2_{a-e}) were converted to corresponding acid hydrizides (3_{a-e}) by reaction with hydrazine hydrate. Five new Schiff bases compounds (4_{a-e}) were prepared by condensing compounds (3_{a-e}) with 4-(N, N – dimethyl amino) benzaldehyde in absolute ethanol. 1, 3, 4 – oxadiazoles – 5 – thiol (5_{a-e}) were synthesized from the reaction of hydrazides (3_{a-e}) with carbon disulfide in alcoholic potassium hydroxide solution. The synthesized compounds are identified on the basis of FT.I.R. spectra analysis, some chemical tests and physical means . The results obtained are compatible with their assigned structures.

Introduction

1, 3, 4- oxadiazole constitutes an important class of compounds having a wide spectrum of biological activity. In the past years, considerable evidence has been accumulated to demonstrate the efficiency of substituted 1, 3, 4- oxadiazole as antibacterial [(1)], antifungal, anti malarial [(2)], anti conversant and anti inflammatory, insecticides compounds[(3)].

The 1, 3, 4- oxadiazole derivatives which contain substitution group in the 2- and 5- positions and specially in the 2- mercapto oxadiazole which contains thioamide group –N–C=S. Its importance lies in removing the poisons in much of the medicine used by human beings [(4 – 6)]. These consideration prompted us to synthesize some novel heterocyclic sulfur – nitrogen containing compounds (Scheme 1).



Scheme 1: Reagents and conditions:

R = H, Ph CH_2-, $(CH_3)_2CH$-, $(C_2H_5CHCH_3)$, $CH_3SCH_2CH_2$-

Step-1; Acetic acid reflux (1 hrs)

Step-2; ethanol / H_2SO_4 reflux, (6 hrs)

.Step-4; ethanol reflux (2 hrs)

Step-5; CS_2 – KOH - ethanol reflux (24 hrs)

Experimental:

Melting points were determined using an electro thermal – 9300 digital melting point apparatus and are uncorrected FT-IR spectra were recorded on 84005 Shimadzu FT-IR Japan, spectrophotometer using KBr disc .

Syntheses of phthalyl amino acids (1_{a-e}) which were prepared by two methods General procedure [7, 8]:

Method a:

An –appropriate amino acid (0.1 mole) was added to a solution of phthalic anhydride (14.8 gm, 0.1mole) in (60ml) acetic acid with stirring, the reaction mixture was heated under reflux for 1hr, then poured over crushed ice with stirring. The precipitate was filtered and recrystallized from ethanol (20%) or acetic acid – water to give the corresponding phthalimides. Physical and spectral date of which are shown in (Table 1).

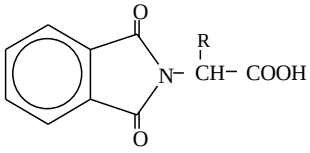


Table (1) : Physical properties of the synthesized compounds (1_{a-e})

Comp. No.	R	M.P. (°C)	Yield (%)	Recryst. Solvent	I.R. – (KBr) - ν (cm^{-1})		
					–C(=O)– amid	–C(=O)– acid	OH
1_a	H	193 – 195 192 – 194	90 %	EtOH	1670	1710	3300
1_b	$PhCH_2$ -	179 – 182 180 – 182	90 %	EtOH	1665	1715	3350
1_c	$C_2H_5-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}$	118 – 120 120 – 122	87 %	EtOH	1670	1720	3380
1_d	$(CH_3)_2CH$	110 – 112 113 – 114	85 %	EtOH	1680	1720	3350
1_e	$CH_3SCH_2CH_2$	123 – 126	80 %	ACOH	1680	1715	3400

Method b:

A mixture of (0.06 mole) of appropriate amino acid and (0.06 mole) of finely grounded phthalic anhydride was heated for (30 min), with stirring in an oil bath at 145-150 °C. After cooling, the solid material was dissolved in (40 ml) of hot methanol, the filtrate solution was diluted with (40 ml) of water, and the product allowed crystallized slowly to give the desired phthalyl amino acids (1_{a-e}) .

Synthesis of Ethyl – N – Phthalyl – 1 – (alkyl or Phenyl) acetate (2_{a-e}) [9]

A mixture of (1_{a-e}) (0.04 mole) in excess ethanol (50 ml) was added (2 ml) concentrated sulfuric acid. The reaction mixture was refluxed for (6 hrs) . The solid separated was filtered, washed with cold water, dried and purified by recrystallization with ethanol to give (2_a) yield 83%, (the solution poured over crushed ice and neutralized by 10% Na_2CO_3, separated organic layer, dried by calcium chloride filtered and purified to give (2_{b-e}) yield(64-70%),. For physical and spectral data see (Table 2).

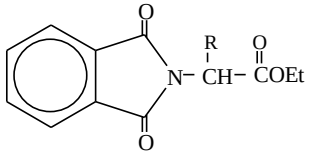


Table (2) : Physical properties of the synthesized compounds (2_{a-e})

Comp. No.	R	M.P. (°C)	Yield (%)	Recryst. Solvent	I.R. – KBr - ν (cm^{-1})		
					–C(=O)– amid	–C(=O)– ester	C-O-C Sym. Asym.
2_a	H	103 – 105	72 %	50% EtOH	1670	1740	1140 1020
2_b	$PhCH_2$ -	Oily	70 %	ACOH	1665	1745	1190 1050
2_c	$C_2H_5-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}$	Oily	69 %	ACOH	1680	1730	1160 1040
2_d	$(CH_3)_2CH$	Oily	64 %	ACOH	1680	1725	1150 1040
2_e	$CH_3SCH_2CH_2$	Oily	70 %	EtOH	1685	1745	1160 1030

Synthesis of N-Phthalyl-amino substituted acetic acid hydrazide (3_{a-e}) [10, 11]

To a solution of compounds (2_{a-e}) (0.04 mole) in EtOH (50ml) and (99%) hydrazine hydrate (0.1mole) (10ml) was added , the reaction mixture was refluxed for 3hrs . after cooling the solid material precipitated was filtered, washed with ethanol and diethyl ether, dried and crystallized using ethanol to give (3_{a-e}) yield (80-90%) . For physical and spectral data see (Table 3).

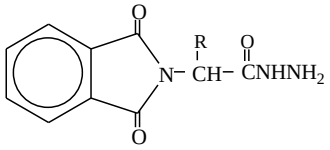


Table (3) : Physical properties of the synthesized compounds (3_{a-e})

Comp. No.	R	M.P. (°C)	Yield (%)	Recryst. Solvent	I.R. – KBr - ν (cm^{-1})		
					–C(=O)– amid	NH_2	C = C
3_a	H	240 d	90 %	EtOH	1680	3300	1600
3_b	$PhCH_2$	255 d	90 %	benzene	1685	3225	1600
3_c	$C_2H_5-\underset{}{\overset{CH_3}{\overset{\vert}{C}}}H$	237 d	87 %	ethylacetate	1660	3250	1600
3_d	$(CH_3)_2CH$	220 d	85 %	EtOH	1660	3350	1600
3_e	$CH_3SCH_2CH_2$	225 d	80 %	EtOH	1675	3300	1600

Synthesis of 2-[*P*-(4-N, N-dimethyl amino benzylidine) N-Phthalyl- substituted ethyl hydrazide] (4_{a-e}) [12]

A mixture of hydrazide (3_{a-e}) (0.005 mole) and 4-(N,N-di methyl) benzaldehyde (0.005 mole, 0.75 gm) in absolute ethanol (50ml) was heated under refluxe for (2 hrs) . The solid obtained after subsequent concentration and cooling was filtered, recrystallization with suitable solvent to give (4_{a-e}) (yield 80 – 90%) For physical and spectral data see (Table 4).

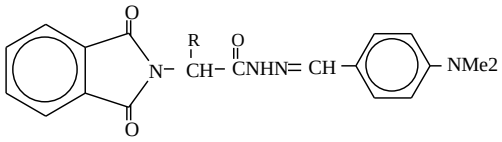


Table (4) : Physical properties of the synthesized compounds (4_{a-e})

Comp. No.	R	M.P. (°C)	Yield (%)	Recryst. Solvent	I.R. – KBr - ν (cm^{-1})		
					–C(=O)– amid	C =N	C – H Arom.
4_a	H	320 – 321	85 %	EtOH	1650	1610	3030
4_b	$PhCH_2$	307 – 308	80 %	EtOH	1670	1615	3100
4_c	$C_2H_5-\underset{}{\overset{CH_3}{\overset{\vert}{C}}}H$	297 – 299	80 %	EtOH	1670	1610	3020
4_d	$(CH_3)_2CH$	283 – 285	80 %	EtOH	1670	1610	3070
4_e	$CH_3SCH_2CH_2$	290 – 292	83 %	ACOH	1660	1625	3030

Synthesis of 1-Phthalyl-1-(5-thiol- 1, 3, 4-oxadiazole- 2-yl) alkane (5_{a-e}) [13]

A mixture of hydrazide (3_{a-e}) (0.005 mole), KOH (0.005 mole) in ethanol (30 ml) and CS_2 (2 ml) was heated under reflux till the evaluation of H_2S (over night). During this time, the odor of hydrogen sulfide was noticeable. The excess solvent was poured in ice cold water and neutralized with dill. HCl the precipitated solid was filtered, washed with water, dried and recrystallized from ethanol. The physical properties of the synthesized are given in (Table 5).

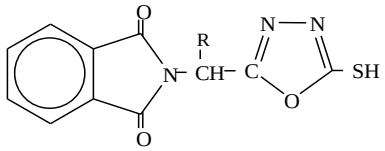


Table (5) : Physical properties of the synthesized compounds (5_{a-e})

Compound No.	R	M.P. (°C)	Yield (%)	Recryst. Solvent	I.R. – KBr - ν (cm^{-1})				
					S – H	C = N	C-O-C Sym. Asym.	C – H Arom.	–C(=O)– amid
5_a	H	286 – 8	75 %	EtOH	2530	1600	1160 1030	3050	1700
5_b	$PhCH_2$	310 – 12	80 %	50% EtOH	2580	1610	1160 1050	3070	1710
5_c	$C_2H_5-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}$	298 – 300	70 %	Aceton	2620	1600	1150 1040	3050	1710
5_d	$(CH_3)_2CH$	292 – 4	70 %	Aceton	2550	1600	1150 1030	3050	1710
5_e	$CH_3SCH_2CH_2$	305 – 7	80 %	EtOH	2590	1610	1160 1040	3040	1720

Results and Discussion:

Fusion of appropriate amino acid with Phthalic anhydride afforded the corresponding Phthalyl amino acids (1_{a-e}) scheme (1) [14]. The structure of the prepared compounds (1_{a-e}) have been identified by their I.R. spectra (Table 1) I.R. spectra showed two bands at (1665 – 1680) cm^{-1}, (1710 – 1720) cm^{-1} and (3350 – 3400) cm^{-1} belong to the presence of C = O and –OH , respectively. Treatment of Phthalyl amino acids (1_{a-e}) with absolute ethanol in the presence of concentrated sulfuric acid give the corresponding Ethyl –N– Phthalyl –1– alkyl / Phenyl glycinate (2_{a-e}). The prepared compounds have been characterized by their I.R. spectra (Table 2). I.R. spectra showed absorption bands near (1205 – 1225) cm^{-1} correspond to the C – O stretching vibrations and two bands at (1665 – 1685) cm^{-1} and (1725 – 1745) cm^{-1} belong to the C = O amide and C = O ester stretching vibrations respectively. The synthesized compounds (3_{a-e}) have been characterized by their physical and spectra data [15] I.R. (Table 3). I.R. spectra showed absorption band (3225 – 3350) cm^{-1} corresponding to NH_2 stretching and one band at (1660 – 1685) cm^{-1} due to C = O amide stretching vibrations. Reaction of these compounds (3_{a-e}) with 4-(N,N Dimethyl amino) benzaldehyde produced Schiff bases (hydrazones). Showed a strong band in the region (1610 – 1625) cm^{-1} as due to C = N stretching vibrations. Finally oxadiazoles derivatives (5_{a-e}) have been prepared by the cyclization reaction of the acid hydrazides (3_{a-e}) with CS_2 – KOH in ethanol [16]. The infrared spectra of compounds (5_{a-e}) (Table 5) showed characterized weak absorption at (2550 – 2620) cm^{-1} corresponding to S – H stretching vibrations. A medium intensity band due to C = N stretching vibrations is appeared at (1600 – 1610) cm^{-1}. This was further confirmed by element test for sulphur. The formation of these condensation products was confirmed by measuring their melting points and spectra analysis.

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تحضير وتشخيص بعض مركبات الهيدرازونات و ٤،٣،١ –اوكسادايازول الجديدة المشتقة من أحماض الفثاليل الامينية

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الملخص:

يتضمن البحث تحضير مشتقات جديدة لفثاليل الأحماض الامينية (1a-e) من تفاعل حامض الفثاليك اللامائي مع حوامض امينية مختلفة، ومن ثم تحويلها إلى الاسترات المقابلة (2a-e) وتم تحويل الاسترات الى مشتق الهيدرازيدات (3a-e) وعند تفاعلها مع المركب 4-(N, N–تنائي مثيل امينو) بنزالديهايد يعطي قواعد شف المقابلة (4a-e).

كذلك تم تحضير مشتقات الاوكسادايازول (5a-e) عن طريق الغلق الحلقي للهيدرازيدات (3a-e) مع CS_2 – KOH . تم تشخيص المركبات المحضرة بالطرق الطيفية والفيزياوية المتاحة وقد دلت النتائج على صحة التراكيب المقترحة.