Chemoselective Synthesis and Reactions of Some New Thiophthalimidines and 3-Ethoxythiophthalimidines

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Abstract

A number of phthalimidines (6) and 3-ethoxyphthalimidines (3) were synthesized by the reduction of the corresponding phthalimides under different conditions. Treatment of the formers with diphosphorous pentasulfide (P_2S_5) in dry dioxane afforded the thio derivatives (7) and (4) respectively. Reaction of (7) and (4) with ethyl amine gave imines (8) and (5), respectively. Hydrolysis of the imines restored the starting (6) and (3).

The structure of all compounds were identified by physical, chemical and spectroscopic data.

الخلاصة

تم تحضير عدد من مشتقات الفثاليميدين (6) و 3-ايثوكسي فثاليميـدين (3) وذلـك بـاختزال الفثاليميدات المقابلة تحت ظروف مختلفة. عومات هذه المركبات الناتجة مع خماسي الكبريت ثنـائي الفسفور (P_2S_5) لتعطي المشتقات الكبريتية للفثاليميدين (7) و 3-ايثوكـسي فثاليميـدين (4) علـى التوالي، والتي عند معاملتها مع اثيل امين أعطت مشتقات الايمين المقابلة (8) و (5). تم الحـصول على المركبات البادئة (6) و (3) من التحلل الحامضي للايمينات المحضرة.

تم تشخيص المركبات المحضرة بواسطة الطرق الفيزياوية والكيمياوية اضافة الـى الطـرق الطيفية المتوافرة.

Introduction

Heterocyclic molecules possessing phthalimidines skeleton have attracted considerable synthetic interests in recent years, as a number of fascinating natural artificial bioactive compounds such as staurosporine, indoprofien and DN-2327 (also known as pazinaclone anxiolytic agent) which have shown clinical utility [1,2,3].

Various methods to the synthesis of phthalimidines were reported in the literatures, some of which were the reaction of phthalaldehyde with aromatic amines in various media [4]. The reaction of phthalaldehyde with phenyl isocyanate [5], as well as the reduction of phthalimides by zinc dust in acidic medium under different conditions [6,7], to obtain phthalimidines or 3-ethoxy phthalimidines.

It seems that little has been published on the synthesis of *N*-substituted thiophthalimidines and *N*-substituted 3-ethoxy thiophthalimidines utilizing diphosphorous pentasulfide (P_2S_5).

Gremlyn [8] has used (P_2S_5) in the preparation of thiosuccinimide. (P_2S_5) was also used in the preparation of pyridine monothioxocarboximide [9].

Although imines can be prepared by different methods [10-14], we herein report a new method to the synthesis of N-substituted imine phthalimidines and N-substituted 3-ethoxy imines phthalimidines via the corresponding thioderivatives.

Experimental

Uncorrected melting points were determined using Gallnkamp melting point apparatus. I.R spectra were recorded by using Pye Unicam SP1100 Spectrophotometer as KBr disc. U.V-Visible spectra were performed on double beam Shimadzu U.V-160 (U.V-Visible) Spectrophotometer. Reactions progress were monitored by the T.L.C technique. Column chromatography was carried out on silica (BDH-60-120). All solvents were purified prior to use.

Synthesis of N-substituted phthalimides (2a-f)
General procedure [9]

An appropriate substituted aromatic amines (0.1 mole) were added to a solution of phthalic anhydride (14 gm, 0.1 mole) in acetic acid with stirring. The reaction mixture was heated under reflux for 1 hr. Water was added to initiate crystallization. Recrystallization from acetic acid-water gave N-substituted phthalimides. Physical and spectral data of the products are shown in Table I.

Synthesis of N-substituted 3-ethoxy-N-substituted phthalimidines (3a-f)
General procedure [9]

Zinc dust (0.02 mole) was added at once with stirring to a solution of an appropriate phthalimides in absolute ethanol (40ml). concentrated hydrochloric acid (5 ml) was added slowly to the reaction mixture until it became clear, then refluxed for 1 hour, cooled and filtered with suction. The mixture was neutralized with sodium hydroxide (20%) and poured into water. The resulting white precipitate was removed by filtration, the filtrate was extracted with chloroform (4 × 30 ml). The combined extracts were washed with water and then dried over anhydrous sodium sulphate. Filtration and concentrated to give 3-ethoxy phthalimidines in a good yields. For physical and spectral data for the products see Table II.

Synthesis of N-substituted phthalimidine (6a-f)
General procedure [9]
a. Direct method

A solution of (0.02 mole) phthalimides in aqueous ethanol (20%) (50 ml) was warmed on a hot plate and zinc dust (1.3 gm) was added with stirring. Concentrated hydrochloric acid (5 ml) was added dropwise to the reaction mixture until it became clear. The reaction mixture was heated under reflux for 2 hrs, cooled and followed by the addition of sodium hydroxide solution (20%) until it became neutral. The resulting white precipitate was removed by filtration and the filtrate was extracted with chloroform (4 × 30 ml). The combine extracts were washed with water (3 × 20 ml), then dried with anhydrous magnesium sulphate. Filtration and concentration gave N-substituted phthalimidines. The physical and spectral data were listed in Table III.

b. Indirect method

A solution of 3-ethoxy-N-substituted phthalimidines (3) (0.02 mole) in aqueous ethanol (20%) (50 ml) was warmed on a hot plate and zinc dust (1.3 gm) was added with stirring. Concentrated hydrochloric acid was added to the reaction mixture until it

became clear. The reaction mixture was heated under reflux with stirring for 3 hrs. Working up as usual gave the N-substituted phthalimidines which was identical to the product isolated in the previous method.

Synthesis of thiophthalimidines (7a-f)
General procedure [9]

A solution of an appropriate N-substituted phthalimidines (6) (0.05 mole) in dry dioxane (50 ml) was stirred and diphosphorous pentasulphide (0.05 mole, 1.1 gm) was added at once. The reaction mixture was heated under reflux with stirring for 1 hr. The reaction mixture was filtered while hot and allowed to cool to room temperature. Evaporation of the solvent to dryness followed by column chromatography of the resulting mass using petroleum ether (40-60 °C)-ethyl acetate 9:1 as eluant gave N-substituted thiophthalimidines (7). Physical and spectroscopic data of the products are listed in Table IV.

Synthesis of 3-ethoxy-thiophthalimidines (4a-f)
General procedure:

Solution of an appropriate N-substituted-3-ethoxy phthalimidines (3) (0.1 mole) in dry dioxane (50 ml) was stirred and diphosphorous pentasulfide (P_2S_5) (22 gm, 0.1 mole) was added at once. The reaction mixture was heated under reflux with stirring for 2 hrs. Working up as usual gave the N-substituted-3-ethoxy thiophthalimidines (4). For physical and spectroscopic see Table V.

Synthesis of imine phthalimidines (8a-f)
General procedure

N-substituted thiophthalimidines (0.05 mole) in dry dioxane (30 ml) were stirred with ethyl amine (0.6 ml, 0.05 mole) for 2 hrs at room temperature. The solvent was evaporated to leave an oil which was loaded on silica column and eluted with petroleum ether (40-60 °C)-ethyl acetate 1:1. This gave a solid material which was crystallized from ether-petroleum ether (40-60 °C). For physical and spectroscopic data see Table VI.

Synthesis of 3-ethoxy imine phthalimidines (5a-f)
General procedure

N-substituted-3-ethoxy-thiophthalimidines (0.05 mole) were stirred in dry dioxane (30 ml) with ethyl amine (0.6 ml, 0.05 mole) for 2 hrs at room temperature. The solvent was evaporated to leave an oil which was loaded on silica column and eluted with petroleum-ether (40-60 °C)-ethyl acetate 50%. This gave a solid material which was crystallized from ether-petroleum ether (40-60 °C). The physical and spectral data were listed in Table VII.

Hydrolysis of imines (5, and 8)

To an ethanolic solution of imines of phthalimidines or 3-ethoxy phthalimidines, concentrated hydrochloric acid (5 drops) was added. The reaction mixture was refluxed for 2 hrs, cooled and evaporated to give 3-ethoxy phthalimidine (3) and phthalimidine (6) which were identical to those prepared in the previous methods.

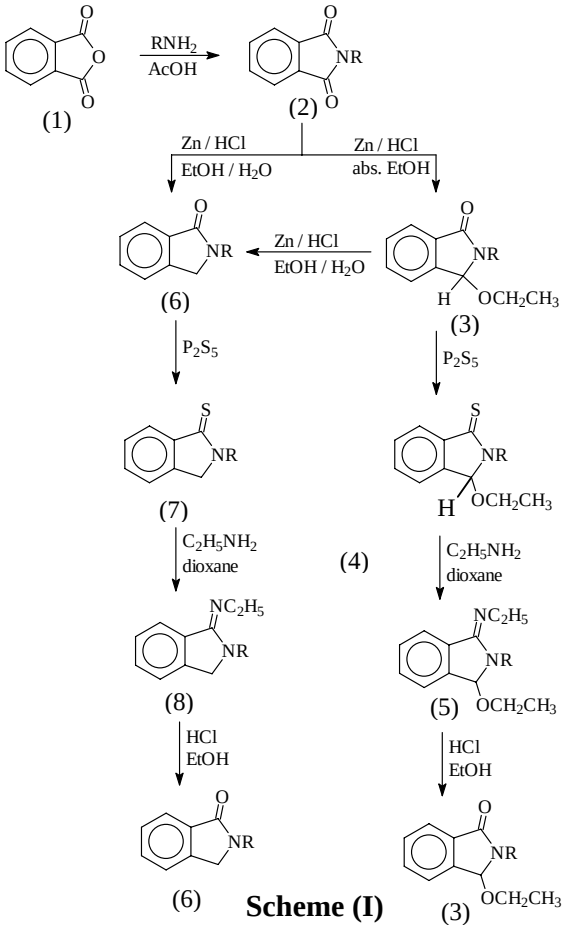
Results and Discussion

a. Preparation of phthalimidines (6) and 3-ethoxy phthalimidines (3)

The synthesis of phthalimidines was carried out following the same procedure adopted for the preparation of N-alkyl phthalimidines and 3-ethoxy phthalimidines [6,7]. The reaction was carried out by treating N-substituted phthalimides (2) and zinc dust in acidic media with either aqueous ethanol (20%) to get the phthalimidines (6) or with absolute ethanol to get 3-ethoxy phthalimidines (3) both in good yields.

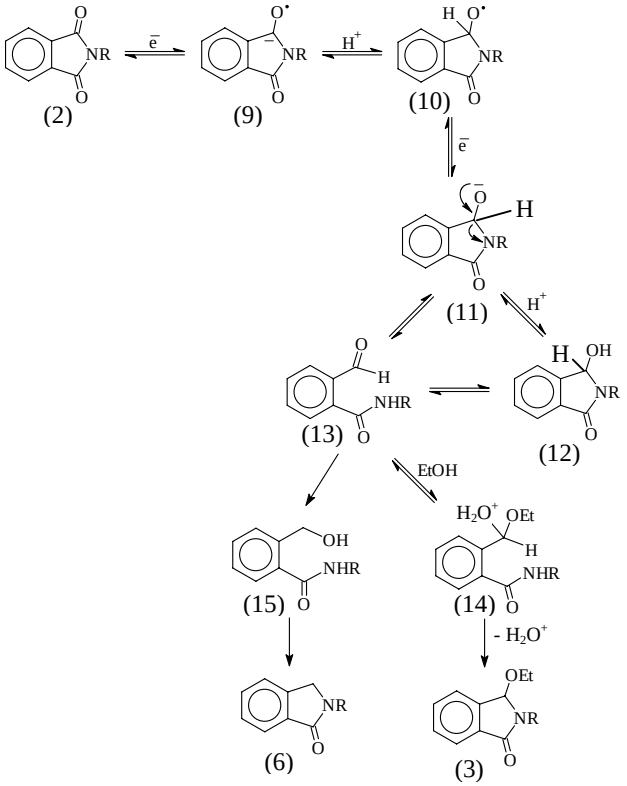
It is worth noticing that, when compound (3) was treated with zinc

dust in aqueous ethanol and concentrated hydrochloric acid, phthalimidines (6) were obtained (Scheme I).



Scheme (I)

reduction of N-substituted phthalimidines is shown in Scheme (II).



Scheme (II)

The structures of phthalimidines were elucidated using spectral and chemical interconversion. The I.R spectral data for compound (6) (Table III) showed an absorption band at (1680-1710 cm^{-1}) due to carbonyl groups and the U.V spectrum showed λ_{max} at (278-299) nm.

The I.R spectra of 3-ethoxy phthalimidines (3) (Table II) showed an absorption bands at around 1710 cm^{-1} due to C=O group and characteristic absorption band at around 1250 cm^{-1} due to ether linkage.

The possible pathway [9] accounting for the formation of N-substituted phthalimidines by zinc

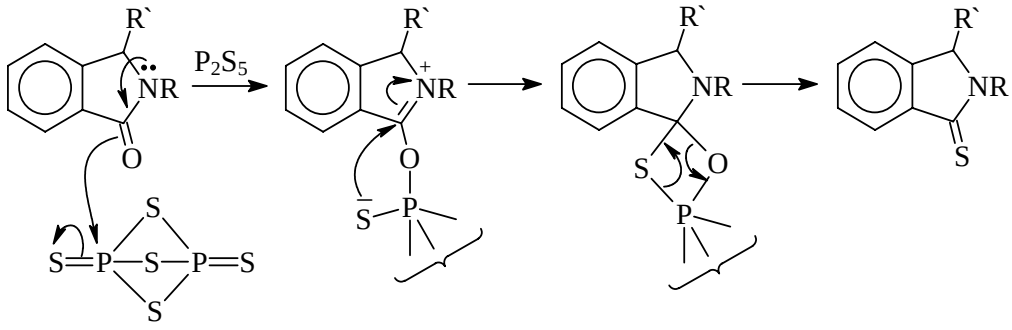
The mechanism begins with gain of electron to give (9). In the presence of acid, protonation can occur on carbon of the carbonyl group to produce the intermediate (10). The next step involves a second addition of electron to give (11) and protonation on oxygen to produce 3-hydroxy-1H-isoindol (12). The ring opened intermediate (13) can be formed from (12) and (13) may react further by way of two routes. Nucleophilic attack of aldehydic group in (13) by one molecule of ethanol would afford the hemiacetal (14) which can cyclise by losing one molecule of water to give substituted 3-ethoxy-1H-isoindol-1-one (3). Further reduction of

the open intermediate (13) can occur to give the compound (15) and then cyclisation with loss of one molecule of water leads to the final product (6).

b. Preparation of thiophthalimidines (7) and 3-ethoxy thiophthalimidines (4)

The next step in the synthetic strategy (Scheme I) was the condensation of phthalimidines (6) and 3-ethoxy phthalimidines (3) with diphosphorous pentasulfide (P_2S_5) in dry dioxane. The structure of thiophthalimidines products were confirmed on the basis of spectral and chemical evidences. The I.R spectra (Tables IV and V) showed absorptions at (1140-1205 cm^{-1}) due to the thione group (C=S) besides the absence of carbonyl group absorption. The U.V spectra showed λ_{max} at (300-388) nm, also sulpher positive test indicate the conversion.

A possible pathway accounting the formation of thiophthalimidine and 3-ethoxy thiophthalimidines is shown in Scheme (III).



Scheme (III)

c. Preparation of imines (8 and 5)

When thiophthalimidines (7) and 3-ethoxy thiophthalimidines (4) were allowed to react with an excess of ethyl amine in dry dioxane at room temperature. Imines were obtained as expected with expulsion of H_2S.

The structure of imines were elucidated by spectroscopic data (Table VI and VII) and by their conversion to the starting phthalimidines (6) and 3-ethoxy phthalimidines (3).

The I.R spectra of those compounds exhibited characteristic bands at (1600-1620 cm^{-1}) due to C=N group with the absence of thione group at (1140-1205 cm^{-1}). This was confirmed by the negative element test for sulfur.

Finally, it is interesting to know that the prepared imines (5 and 8) were hydrolysed with ethanol in acidic medium to give products which were identical to the starting phthalimidines (6) and 3-ethoxy phthalimidines (3).

Table (I): Physical and spectroscopic data of phthalimides (2a-f)

Comp. 2	R	Molecular formula	m.p. °C	Yield %	I.R (cm^{-1}) KBr disc			U.V. EtOH
					ArC-H	C=O	C=C	λ_{max} (nm)
a	C_6H_5	$C_{14}H_9NO_2$	202-204	85	3010	1708	1605	294,278,274
b	o-ClC_6H_4	$C_{14}H_8ClNO_2$	154-156	87	3000	1710	1600	293,274,247
c	m-ClC_6H_4	$C_{14}H_8ClNO_2$	144-146	90	3020	1700	1608	299,250,225
d	3-NO_2-4-ClC_6H_3	$C_{14}H_7ClN_2O_2$	215-218	91	3020	1710	1605	300,294,240
e	o-$CH_3C_6H_4$	$C_{15}H_{11}NO_2$	162-164	85	3010	1690	1600	290,261,225
f	C_5H_4N	$C_{13}H_8N_2O_2$	191-193	81	3000	1720	1610	292,258,235

Table (II): Physical and spectroscopic data of 3-ethoxy phthalimides (3a-f)

Comp. 3	R	Molecular formula	m.p. °C	Yield %	I.R (cm^{-1}) KBr disc					U.V. EtOH
					ArC-H	C=O	C=C	C=N	C-O	λ_{max} (nm)
a	C_6H_5	$C_{16}H_{15}NO_2$	128-131	72	3100	1710	1610	1615	1250	288,275,232
b	o-ClC_6H_4	$C_{16}H_{14}ClNO_2$	168-169	58	3020	1720	1600	1610	1265	293,275,247
c	m-ClC_6H_4	$C_{16}H_{14}ClNO_2$	142-144	66	3000	1700	1620	1600	1255	290,265,225
d	3-NO_2-4-ClC_6H_3	$C_{16}H_{13}ClN_2O_2$	56-58	35	3010	1710	1610	1601	1275	280,258,215
e	o-$CH_3C_6H_4$	$C_{17}H_{17}NO_2$	276d	41	3000	1710	1610	1620	1250	274,247,222
f	C_5H_4N	$C_{16}H_{14}N_2O_2$	92-94	56	3020	1720	1620	1600	1270	292,250,234

Table (III): Physical and spectroscopic data of phthalimidines (6a-f)

Comp. 6	R	Molecular formula	m.p. °C	Yield %	I.R (cm^{-1}) KBr disc			U.V. EtOH
					ArC-H	C=O	C=C	λ_{max} (nm)
a	C_6H_5	$C_{14}H_{11}NO$	158-160	67	3010	1690	1610	278,272,227
b	o-ClC_6H_4	$C_{14}H_{10}ClNO$	52-54	43	3030	170	1600	288,275,232
c	m-ClC_6H_4	$C_{14}H_{10}NO$	143-145	70	3020	1702	1590	280,275,225
d	3-NO_2-4-ClC_6H_3	$C_{14}H_9N_2O$	39-42	79	3000	1680	1610	299,274,247
e	o-$CH_3C_6H_4$	$C_{15}H_{13}NO$	71-73	57	3000	1690	1590	281,258,235
f	C_5H_4N	$C_{13}H_{10}N_2O$	146-148	70	3010	1725	1670	290,261,225

Table (IV): Physical and spectroscopic data of thiophthalimidines (7a-f)

Comp. 7	R	Molecular formula	m.p. °C	Yield %	I.R (cm^{-1}) KBr disc			U.V. EtOH
					ArC-H	C=C	C=S	λ_{max} (nm)
a	C_6H_5	$C_{14}H_{11}NS$	155-157	66	3020	1600	1170	346,291,239
b	o-ClC_6H_4	$C_{14}H_{10}ClNS$	114-116	55	3010	1590	1201	366,288,243
c	m-ClC_6H_4	$C_{14}H_{10}ClNS$	169-171	59	3000	1590	1175	316,272,239
d	3-NO_2-4-ClC_6H_3	$C_{14}H_9ClN_2OS$	215-218	63	3000	1610	1160	332,295,234
e	o-$CH_3C_6H_4$	$C_{15}H_{13}NS$	191-193	65	3050	1600	1172	336,300,245
f	C_5H_4N	$C_{13}H_{10}N_2S$	140-142	50	3000	1600	1152	388,272,222

Table (V): Physical and spectroscopic data of 3-ethoxy thiophthalimidines (4a-f)

Comp. 4	R	Molecular formula	m.p. °C	Yield %	I.R (cm^{-1}) KBr disc				U.V. EtOH
					ArC-H	C=C	C-O	C=S	λ_{max} (nm)
a	C_6H_5	$C_{15}H_{14}NOS$	75-77	63	3010	1608	1245	1180	331,297,234
b	o-ClC_6H_4	$C_{16}H_{13}ClNOS$	188-190	59	3020	1590	1255	1140	346,291,269
c	m-ClC_6H_4	$C_{16}H_{13}ClNOS$	179-180	55	3000	1600	1275	1170	335,300,246
d	3-NO_2-4-ClC_6H_3	$C_{16}H_{13}ClN_3OS$	130-132	66	3010	1610	1270	1190	300,247,222
e	o-$CH_3C_6H_4$	$C_{17}H_{16}NOS$	127-129	59	3000	1600	1250	1175	316,290,239
f	C_5H_4N	$C_{14}H_{14}N_2OS$	200-203	60	3000	1600	1255	1190	310,293,234

Table (VI): Physical and spectroscopic data of imine thiophthalimidines (8a-f)

Comp. 8	R	Molecular formula	m.p. °C	Yield %	I.R (cm^{-1}) KBr disc			U.V. EtOH
					ArC-H	C=C	C=N	λ_{max} (nm)
a	C_6H_5	$C_{14}H_{11}NS$	134-136	71	3010	1590	1620	510,348,229
b	o-ClC_6H_4	$C_{14}H_{10}ClNS$	122-124	70	3000	1580	1600	502,292,216
c	m-ClC_6H_4	$C_{14}H_{10}ClNS$	108-112	63	3050	1590	1610	500,284,267
d	3-NO_2-4-ClC_6H_3	$C_{14}H_9ClN_2OS$	168-171	71	3020	1585	1600	520,278,248
e	o-$CH_3C_6H_4$	$C_{15}H_{13}NS$	91-93	60	3000	1588	1605	510,403,219
F	C_5H_4N	$C_{13}H_{10}N_2S$	155-157	75	3050	1590	1600	626,348,216

Table (VII): Physical and spectroscopic data of 3-ethoxy imine thiophthalimidines (5a-f)

Comp. 5	R	Molecular formula	m.p. °C	Yield %	I.R (cm^{-1}) KBr disc				U.V. EtOH
					ArC-H	C=C	C=N	C-O	λ_{max} (nm)
a	C_6H_5	$C_{16}H_{20}N_2O$	151-153	60	3000	1565	1620	1255	570,287,229
b	o-ClC_6H_4	$C_{16}H_{19}ClN_2O$	83-85	69	3050	1590	1600	1268	510,261,245
c	m-ClC_6H_4	$C_{16}H_{19}ClN_2O$	91-93	70	3010	1580	1610	1250	504,400,248
d	3-NO_2-4-ClC_6H_3	$C_{18}H_{18}ClN_3O_3$	64-66	74	3100	1589	1601	1240	500,334,219
e	o-$CH_3C_6H_4$	$C_{19}H_{22}N_2O$	122-124	63	3010	1582	1620	1262	501,261,253
f	C_5H_4N	$C_{17}H_{19}N_3O$	168-170	68	3000	1590	1605	1270	510,490,295

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