Synthesis of Some Diazole, Triazole and Tetrazole Compounds via Imide Intermediate

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Abstract

Some open chain compounds (5,6) and pyrazole (12,16) imidazole, triazole (7,9) and tetrazole (4) compounds were synthesized using phthalimide glycine derivatives as starting materials, they were converted into substituted acetamide or acetimidoyl chloride derivatives which were cyclized into the coresponding heterocyclic compounds using either alcoholic potassium hydroxide or phosphorous chloride and phenacyl bromide respectively. The final compounds were characterized using their melting points and the infrared spectroscopy.

الخلاصة

تم تحضير عدد من المركبات المفتوحة السلسلة (5، 6) ومركبات البايرازول والاميدازول (12، 16) والترايازول (7، 9) وكذلك التترازول وهو المركب (4) وذلك باستعمال بعض مشتقات فثاليميد الكلايسين كمواد اولية في التحضير. تم تحويل هذه المشتقات الى معوضات اميد الخليك او كلوريد اميد الخليك تم بعد ذلك حولفة تلك الكلوريدات الى مركبات حلقية مقابلة وذلك اما باستعمال محلول هيدروكسيد البوتاسيوم الكحولي او باستعمال خامس كلوريد الفسفور وبروميد الفيناسيل على التوالي. تم تشخيص النواتج النهائية باستعمال درجات الانصهار وكذلك باستعمال طيف الاشعة تحت الحمراء.

Introduction

There has been considerable efforts in the chemistry of carbon nitrogen bond including the formation of this type of compounds and some of their reactions with versatile compounds[1]. Among the published methods for the formation of -C=N- bond were; reactions of carbonyl compounds with amino groups and related reaction[2-5]. Reaction of aromatic nitroso compounds with active methylene groups (Ehrlichschs reaction)[6]. Reaction of aliphatic compounds containing an active methylene group couple with diazonium salts to form aryl hydrazones[7,8]. Addition of acetylenic compounds to carbon-carbon double or triple bonds[9,10]. Formation the -C=N- bonds through yields[11-13]. Tautomerization of amides and

thioamides and related reactions[14-16]. Addition reactions to nitriles, isonitriles, nitrile oxides and related compounds[17-19] and the oxidation and elemination from nitrogen compounds[20-22]. The synthesis of imidoyl chloride compounds from the reaction of anilides and phosphorous pentachloride was first invistigated by Sonn, Muller and Mosetting[23,24].

Recent works including the synthesis of imides by chemical reduction of 3-amino benzoxazol-2-ene[25], dehydration of amides by phosphorous pentaoxide[26] and the synthesis of (-) coniine[27]. The synthesis of 3-amino-2-alkenoates was carried out by the reaction of the corresponding ester with nitriles[28-31]. Among the reactions of imides are; The synthesis of four, five and six membered ring heterocyclic compounds[33]. It was found that the reaction of imidoyl chloride with aliphatic amines gaves the corresponding imidines[34]. The recent works on the cycloaddition of imides including, synthesis of some 3-aryl-1,2,4-oxadiazole carring a protected L-alanine side chain[35], synthesis and characterization of an insuline-Minetic disaccharide[36], the synthesis and phenotypic screning of guanine-Minetic livrary[37] and the synthesis of substituted pyridinones by multicomponent coupling processes[38].

According to the above important applications of the imide compounds we investigate the synthesis of some open chain compounds together with the synthesis of heterocycluc compounds including imidazole, pyrazole, triazole and tetrazole compounds. Our next goal is to find a biological application of the above synthesized compounds.

Experimental

All melting points were uncoorected using Electrothermal 9300 Apparatus, IR spectra were performed using Infrared Spectrophotometer Model Tensor 27 Bruker Co., Germany, as KBr disc. Glycylphthalimide was prepared according to literature procedure[36].

Synthesis of α-phthalimido-N-(4-nitrophenyl) acetamide (2)[39]:

Compound (1), (20.5 g, 0.1 mole) and thionyl chloride (11.8 g, 0.1 mole) were mixed together and gently warmed for 2 hrs., followed by the addition of 4-nitroaniline (1.38 g, 0.01 mole) in 50 ml of dry THF with continuous stirring. After complete addition, the reaction mixture was refluxed for additional one hr., cooled and the solvent was then evaporated under reduced pressure. Recrystallization of the residue from ethanol gave yellow crystals, m.p. 234-235 °C, Table (1).

Synthesis of N-(4-nitrophenyl)-α-phthalimido acetimidoyl chloride (3)[40]:

Compound (2), (3.5 g, 0.01 mole) and phosphorous pentachloride (2.08 g, 0.01 mole) were mixed together under unhydrous condition. The mixture was heated for 30 min. at 110 °C, then the reaction temperature was raised to 160 °C until the evolution of hydrogen chloride ceased (about 0.5 hr). Distillation of the resulted phosphorous oxychloride under reduced pressure gave crude product which recrystallized from benzene. The melting point of the final pure compound was 204 °C dec., Table (1).

Synthesis of 5-phthalimido methyl-1-(4-nitrophenyl)-tetrazole (4)[41]:

A mixture of (1.54 g, 0.005 mole) of compound (3) and NaN_3 (0.32 g, 0.005 mole) in 20 ml ethanol was refluxed for 2 hrs., cooled, filtered off and recrystallized from ethanol afforded yellow prisms crystals, m.p. 254-256 °C, Table (1).

Synthesis of N-(4-nitrophenyl)-N-substituted-α-phthalimido acetimidine hydrochloride (5a-d)[42]:

A mixture of aliphatic amine (0.01 mole) in dry pyridine (50 ml) was added to compound (3) (3.08 g, 0.01 mole) with continuous stirring. The reaction mixture was heated at 160 °C for about 20 min., cooled and 20 ml of water was then added. The resulted precipitate was recrystallized from ethanol giving colourless crystals. The melting points, yield are represented in Table (1).

Synthesis of N-(4-nitrophenyl)-N-substituted-α-phthalimido acetamidine (6a,b)[42]:

A mixture of substituted hydrazine (0.01 mole) in 50 ml dry pyridine was added to compound (3) (3.089, 0.01 mole) with continuous stirring then refluxed for 20 min., cooled and worked up as in compounds (5a-d) above. Recrystallization from ethanol gave colourless crystals of compounds (6a,b) as indicated in Table (1).

Synthesis of 5-phthalimidomethyl-4-(4-nitrophenyl)-3-substituted-1,2,4-triazole (7a,b)[43]:

Compound (6a or b) (0.005 mole) was refluxed with 5% alcoholic potassium hydroxide solution (20 ml) for 12 hrs. The reaction mixture was then cooled and filtered off, neutralized with 5% aqueous acetic acid solution. The solid product was recrystallized from ethanol to afford the titled compounds as colourless crystals, other physical properties are presented in Table (1).

Synthesis of N-(4-nitrophenyl)-N-substituted-α-phthalimido acetimidine (8)[42]:

Compound (3), (3.08 g, 0.01 mole) and ethyl carbazate (1.04 g, 0.01 mole) in dry pyridine (50 ml) were treated as in compound (5a-d) and worked up as in the synthesis of the compounds above giving compound (8) with mp 188-190 °C, Table (1).

Synthesis of 4-(4-nitrophenyl)-5-phthalimidomethyl-1,2,4-triazole-3-one (9)[43]:

A mixture of compound (8), (4.1 g, 0.01 mole) in 5% alcoholic potassium hydroxide solution (25 ml) was refluxed for 12 hr, worked up as in preparation of (7a-d) procedure above. The final compound was recrystallized from ethanol to give white crystals, m.p.> 300 °C, Table (1).

Synthesis of (α-phthalimido-N-phenyl) acetyl hydrazide (10)[39]:

Thionyl chloride (1.18 g, 0.05 mole) was dropwise added to phthalyl glycine (2.05 g, 0.05 mole). The reaction mixture was gently heated for 2 hrs., cooled and 50 ml of dry THF was then added. The final mixture was dropwise added to a solution of phenyl hydrazine (5.3 g, 0.05 mole) in 50 ml pyridine with continuous stirring. After about 2 hrs., the reaction mixture poured on to crushed ice (about 100 g). The resulted hydrazide was collected and recrystallized from ethanol giving yellow crystals with melting point of 182-183 °C, Table (1).

Synthesis α-phthalimido-N-phenylamino acetimidoyl chloride (11)[44]:

Compound (10), (14.75 g, 0.05 mole) and phosphorous pentachloride (10.42 g, 0.05 mole) in 25 ml of dry ether were refluxed for 24 hrs. under anhydrous condition. After the reaction has been completed it was cooled and a solution of 15 g of phenol in a mixture of dry ether (25 ml) and methanol (40ml) was then added. The solvent was evaporated under reduced pressure using rotary evaporated to half its volume. The final mixture was left in cool box for 5 days. The product was separated as prisims crystals with melting point 160-162 °C, Table (1).

Synthesis of 1-phenyl-3-phthalimidomethyl-5,5-disubstituted-2-pyrazoline (12a-c):

A mixture of the corresponding olefin (0.1 g, 0.01 mole), hydroquinone (0.1 g, 0.01 mole) and compound (11) (2.99 g, 0.01 mole) and triethyl amine (2.02 g, 0.02 mole) in 50 ml dry benzene was refluxed at 100 °C for 2 hrs. with continuous stirring. The hot solution was filtered off and the filtrate was rotary evaporated. The residue was crystallized from methanol giving prisms crystals, their melting points are indicate in Table (1).

Synthesis of α-phthalimido acetamide (13)[39]:

Phthalyl glycyl chloride (5 g, 0.022 mole) was added to saturated ammonium hydroxide solution (12 g, 100 ml) with continuous stirring for 1 hr. The product was filtered off, washed with water then recrystallized from ethanol to afford the acetamide(13) as white needls, m.p.257-258 °C, Table (1).

Synthesis of ethyl α-phthalimido acetamidate hydrochloride (14)[45]:

Compound (13), (0.02 mole) was heated in water bath at 40-45 °C for half hour, then ethyl chloroformate (0.02 mole) was added rapidly. The reaction mixture was stirred for 30 min., filtration of the product and washed with dry ether and dried in air atmosphere gave white crystals, m.p. 235-236 °C, Table (1).

Synthesis of amino α-phthalimido-N-benzamido acetamide (15)[46]:

A mixture of compound (14) (2.95 g, 0.01 mole) and benzoyl hydrazide (1.36 g, 0.01 mole) and triethyl amine (1.01 g, 0.01 mole) in 40 ml ethanol was mixed together. The reaction mexture was refluxed for 2 hrs., cooled and filtered off. The residue was recrystallized from water and the pure product had m.p. 210-212 °C, Table (1).

Synthesis of 2-phthalimido-3-N-benzamido-4-3H-imidazole (16)[46]:

To compound (15) (2.99 g, 0.01 mole) in 10 ml ethanol, a mixture of (1.99 g, 0.01 mole) phenacyl bromide and triethyl amine (1.01 g, 0.01 mole) in 20 ml ethanol in one portion was added. The reaction mixture was refluxed for 18 hrs., cooled and filtered off. The solid product was recrystallized from ethanol to give white crystals, m.p. 272 d., Table (1).

Results and Discussion

As it was mentioned in the introduction there were different methods for the preparation of imidoyl chloride among which is the conversion of the coresponding amide using PCl_5 as chlorinating and dehydrating agent. Scheme (1) shows this transformation into compound (3) which was characterized by the main absorption bands as indicated in Table (1). Compound (3) was cyclized by sodium azide into the corresponding tetrazole derivative (4). Compounds (5) were obtained as hydrochloride salt upon treatment of compound (3) with amines. These open chain compounds represented the substituted imidoyl hydrochlorides (5a-d) and characterized by $-NO_2$ stretching bands at 1255-1299 cm^{-1}, 1508-1592 cm^{-1} respectively, C=C of the aromatic ring absorbed at 1487-1610 cm^{-1}, -C=N- absorbed at 1611-1681 cm^{-1} and the CON of (νC=O) phthalimide group was basorbed as two bands one belongs to symmetric, the other for asymmetric stretching vibration (Table 1). Compounds (6,8) were obtained as acetimidine derivatives (Scheme 1) their IR specta (Table 1) indicate the presence of the precursor phthalimide moiety through their carbonyl absorption as indicated in the Table, and he acetimidine absorption at 1616-1638 cm^{-1} in which compound (6a) shows single broad band belongs to

symmetric stretching while the asymmetric one may be hidden under the aromatic C=C stretching region.

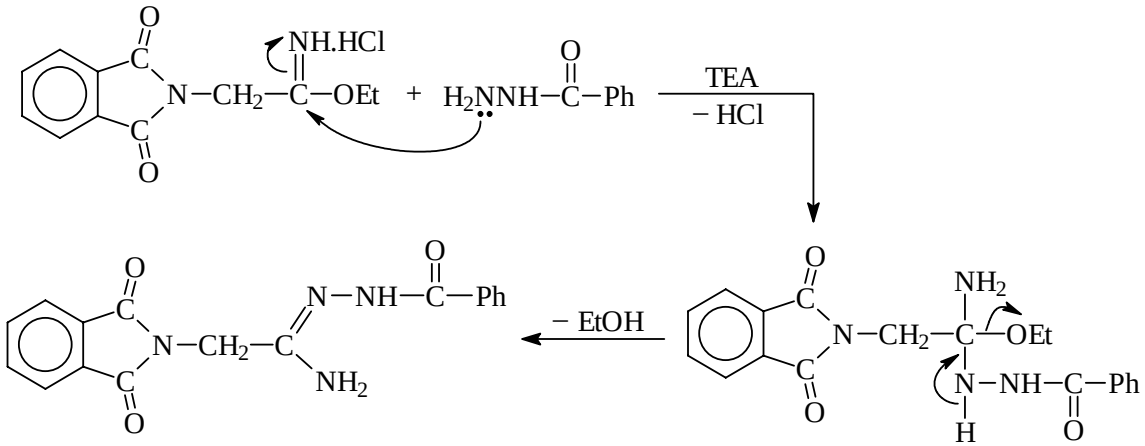
Compound (8) shows amide I and II bands absorbed at 1611 and 1595 cm^{-1} respectively together with the ester carbonyl group absorbed at 1676 cm^{-1}. the other absorption band for the two compounds (6,8) were shown in Table (2). Treatment of compound (6) with alcoholic KOH solution afforded compound (7) as tetrazole derivatives. Their main absorption bands are indicated in Table (1). Compound (9) was synthesized by nucleophilic attack of aniline moiety on the carbonyl carbon of compound (8) then tautomerized into the triazolon which was characterized by the combination of CON, C=C, NO_2, C=N and C=O as indicated in Table (1).

Compounds (10,11) are intermediates for the pyrazoles (12a-c) as shown in Scheme (2) their characteristic absorption bands are indicated in Table (1). Sometimes the amide 2nd band appeared within the aromatic absorption of C=C stretching region. Compounds (13,14 and 15) are intermediates of compound (16) through multistep synthesis[37] as shown in Scheme (2). The final compound (16) was characterized by the following absorption bands which was indicated in Table (1), 1556, 1493 cm^{-1} for the aromatic C=C stretching absorption, 1662 cm^{-1} as broad band for amide 1st band while the amide 2nd band appeared within the aromatic C=C stretching band. The -C=N stretching was appeared as broad band at 1662 cm^{-1}. The carbonyl groups of the phthalimide moiety appeared as broad band (not resolved due to sample concentration) at 1771 cm^{-1}.

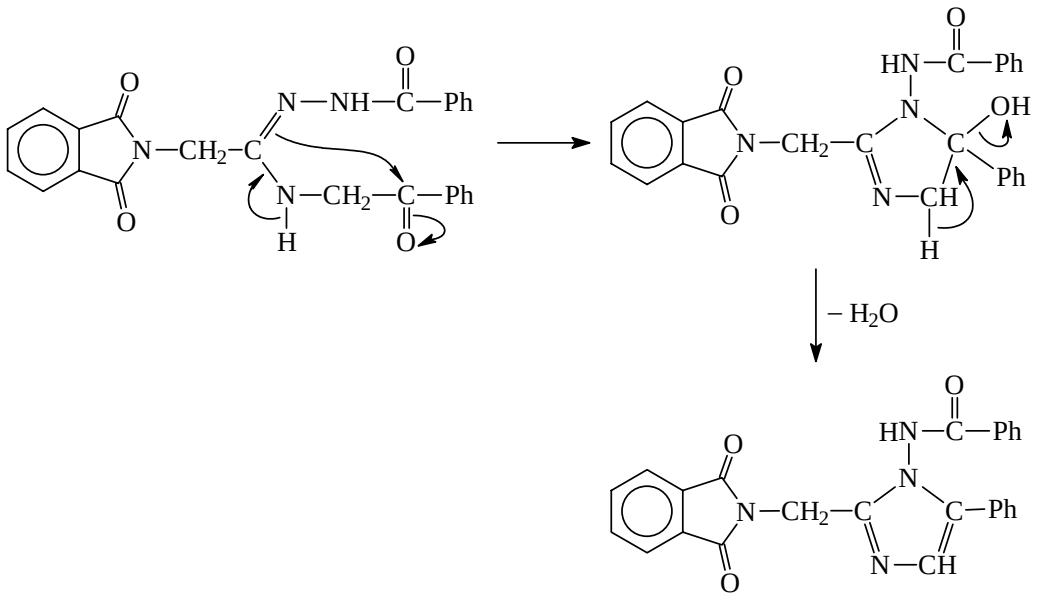
The cyclization mechanism for the formation of compound (4) is simillar to the known one[38] in which the azide group substitute the chloride in imidoyl chloride by simple nucleophilic substitution followed by cyclization. The cyclization of compound (6) into compound (7) was occurred through nucleophilic attack of anilinum ion toward the carbonyl of adjacent hydraizde followed by elimination of H_2O from the intermediate enol form.

The cyclization mechanism for the formation of compound (12) from compound (11) could be represented by simple addition of N-phenyl imidoyl chloride moiety (anilinum ion proton) on the alkene double bond followed by nucleophilic substitution of the formed enolate ion to the chloride of the above moiety.

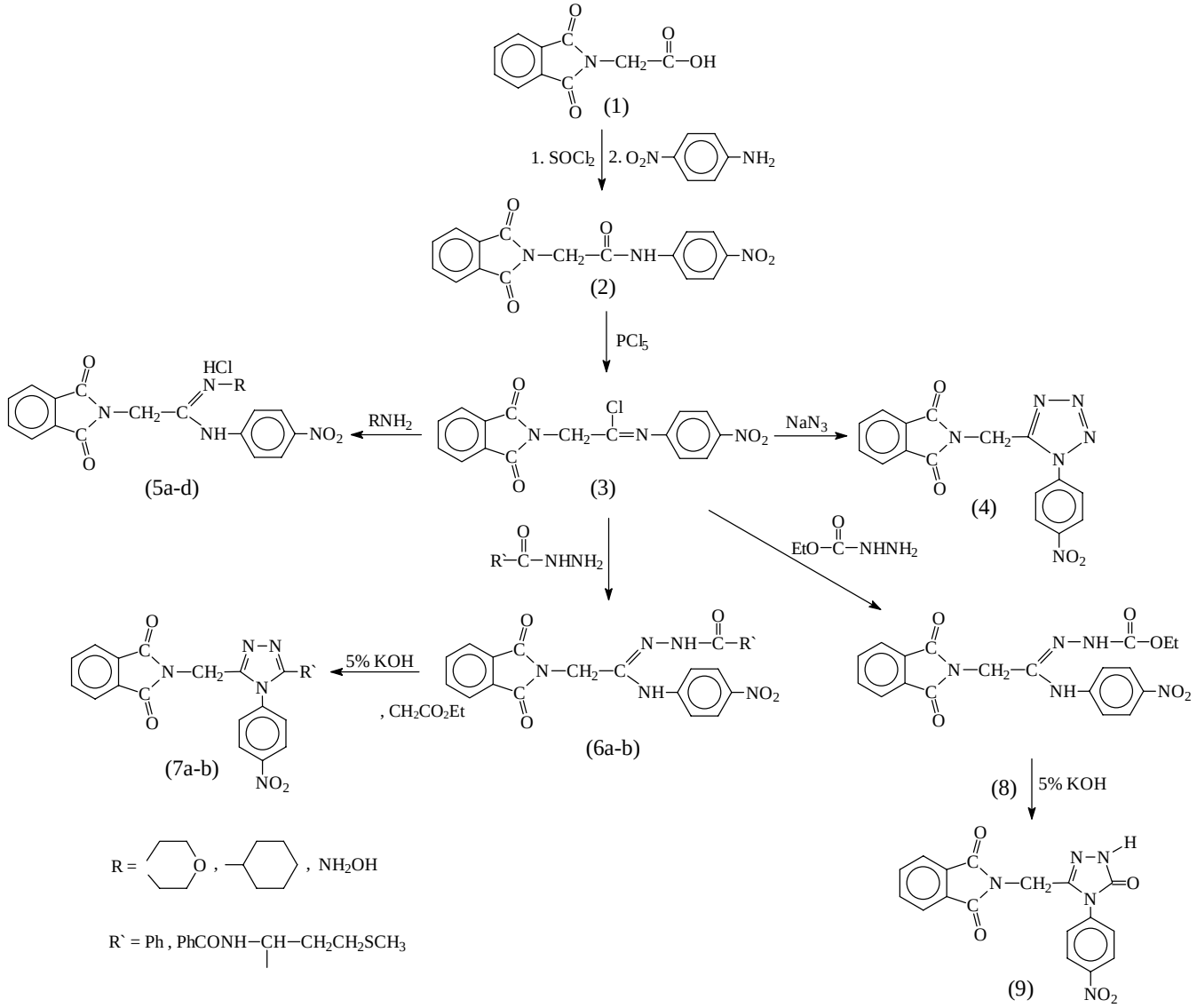
Compound (14) was reacted with phenyl hydrazide to giving compound (15) according to the following proposed mechanism:



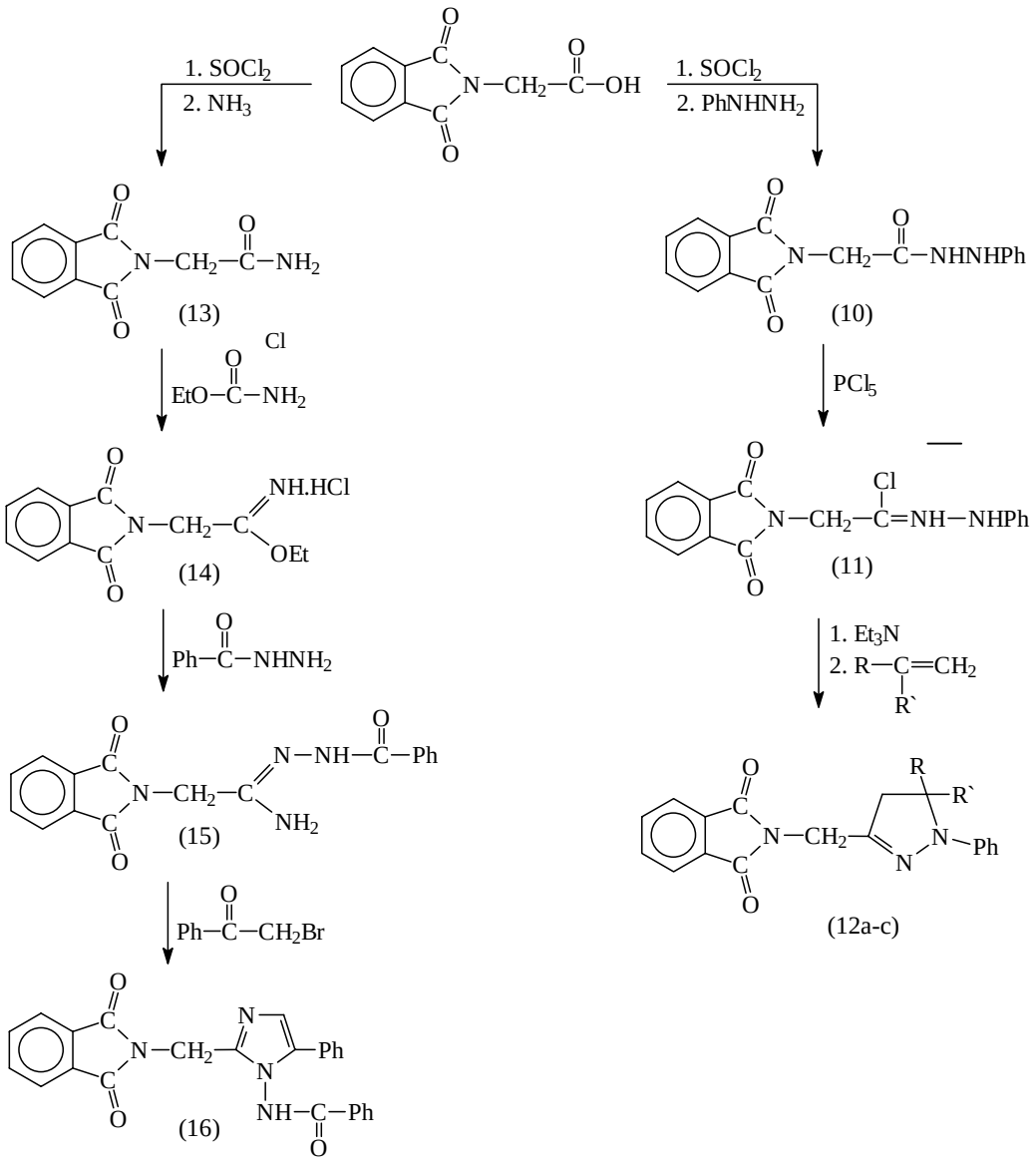
Compound (16) was formed by addition of phenacyl bromide to compound (15) by simple nucleophilic substitution reaction of the amino group to bromine in phenacyl bromide followed by nucleophilic attack of nitrogen toward the carbonyl as illustrated below:



(16)


(1)
1. SOCl2
2. O2N-NH2
(2)
PCl5
(3)
RNH2
(5a-d)
NaN3
(4)
R`-C(=O)-NHNH2
EtO-C(=O)-NHNH2
5% KOH
, CH2CO2Et
(6a-b)
(7a-b)
(8)
5% KOH
(9)
R = O , , NH2OH
R` = Ph , PhCONH-CH(CH2CH2SCH3)

Scheme (1)



R	**R`**
-CH_3	-CO_2CH_3
-H	-CN
-H	-Ph

Scheme (2)

Table (1): IR spectra and physical properties of compounds (2-16)

Comp. No.	m.p. °C	Yield %	IR ν cm^{-1}					
			N-O N=O	C=C Ar	CONH	C=N	CON	NH
2	234-235	86	1220 1490	1599 1490	1633 1557	-	1712 1661	3352
3	204d	69	1267 1510	1610 1495	-	1620	1717 1640	-
4	254-256	82	1218 1508	1596 1500	-	1676 1616	1776 1673	-
5a	172-174	67	1255 1508 1110 C-O	1596 1500	-	1624	1714 1617	3284
5b	245-246	72	1257 1542	1590 1542	-	1632	1770 1707	3287
5c	115-117	54	1299 1505	1598 1505	-	1632	1772 1716	3361
5d	138-140	65	1272 1515	-	1636 1681 ester	1636	-	3296
6a	133-135	76	1214 1487	1607 1487	1638(b)	1607	1717 1638(b)	3246
6b	240-241	61	1299 1508	1597 1632	1683 1597	1632	1774 1714	3479
7a	209-211	52	1254 1508	1595 1558	-	1610	1773 1771	-
7b	256d	44	1299 1520	1595 1559	1676 1508	1616	1773 1711	3280
8	188-190	73	1194 1498	1595 1508	1611 1676 ester	1628	1774 1676	3283
9	> 300	57	1256 1469	1595 1560	1701 1676	1617	1773 1711	3279
10	182-183	80	-	1603 1495	1684 1595	-	1774 1713	3320
11	160-162	71	-	1600 1508	-	-	1770 1706	3270
12a	250-252	68	-	1557 1508	1716 Ester	1557	1773 1732	-
12b	92-94	61	-	1559(b)	2244(b) C≡N	1638(b)	1746	-
12c	152-153	67	-	1600(b) 1541	-	1600(b)	1762 1731	-
13	257-258	90	-	1573 1484	1651 1529	-	1770 1651	3407(b)
14	235-236	79	1116 C-O	1470(b)	-	1617	1773 1758(b)	3415(b)
15	210-212	72	-	1490(b)	1770(b) C=O	1667(b)	1770(b)	3420(b)
16	272d	64	-	1556 1493	1662(b) 1556	1662(b)	1771 1662	3212(b)

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