Synthesis Of 2-Benzamidomethyl-5-Substituted Amino-1,3,4-Thiadiazoles-2,5-Disubstituted 1,3,4-Oxadiazole and 4,5-Disubstituted 1,2,4-Triazole-3-Thiol

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Received 08 / 05 / 2011 **Accepted** 01 / 06 / 2011

الخلاصة

تم في هذا البحث تحضير عدد من معوضات ٤,٣,١- اوكسادايازول، ٤,٢,١- ترايازول من الأحماض الامينية وكلوريد البنزويل. أعطت مفاعلة الحامض الاميني (كلايسين او الآلانين) مع كلوريد البنزويل بوجود كربونات الصوديوم كيتو-اسيد(٢,١) والذي تم تحويله الى اوكسازولينون (٤,٣) من خلال تفاعله مع انهيدريد ألخليك. أعطى تفاعل (٤,٣) مع الهيدرازين المائي-هيدرازيد الحامض (٦,٥). تم تحويل هيدرازيد الحامض (٦,٥) إلى معوضات الثايوسيميكاربازايد (٨,٧) من خلال تفاعله مع ايسوثايوسيانات الفنيل. تم مفاعلة معوضات الثايوسيميكاربازايد مع هيدروكسيد الصوديوم وحامض الكبريتيك المركز لتعطي ٤,٢,١-ترايازول معوض (١٠,٩) 4,3,1- ثايادايازول معوض (١٢،١١) على التوالي. بينما اعطى تفاعل (٧) مع اوكسيد الزئبق 4,3,1- اوكسادايازول (١٣). أعطت تفاعل 4,2,1- ترايازول (١٠،٩) مع ٤-هيدروكسي بنزالدهيد معوضات الترايازول (١٥،١٤). حضر ثايوسيميكاربازايد (١٦) من هيدرازيد الحامض (٥) وتم حولقته بمحاول هيدروكسيد الصوديوم إلى ٥-معوض 4,2,1- ترايازول-٣- ثايول (١٧). شخصت المركبات المحضرة بالطرق الفيزياوية والطيفية.

Abstract

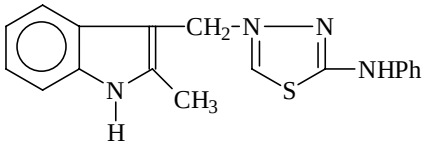
In this paper the synthesis of some substituted 1,3,4-oxadiazoles , 1,3,4-thiadiazoles and 1,2,4-triazoles starting from amino acid and benzoyl chloride is reported. Treatment of glycine or alanine with benzoyl chloride in presence of sodium carbonate gave keto-acid(1,2), which were converted to oxazolinone (3,4) by their reaction with acetic

anhydride. Oxazolinone (3,4) were treated with hydrazine hydrate to give acid hydrazides (5,6). Acid hydrazides were converted to substituted thiosemi- carbazides (7,8) by their reaction with phenyl isothiocyanate. Substituted thiosemicarbazides (7,8) were treated with sodium hydroxide and concentrated sulphuric acid give substituted 1,2,4-triazoles (9,10), 1,3,4-thiadiazoles (11,12) respectively while treatment of (7) with mercuric oxide gave 1,3,4-oxadiazoles (13). Treatment of triazoles (9,10) with 4-hydroxybenzaldehyde gave substituted triazoles (14,15). 1-Substituted thiosemicarbazide (16) was obtained from acid hydrazide (5), cyclized with sodium hydroxide to 5-Substituted-1,2,4-triazole-3-thiol (17). The structures of the synthesized compounds were confirmed by physical and spectral means.

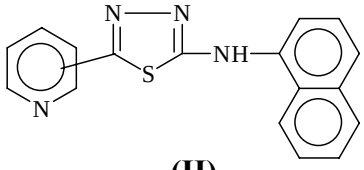
Introduction

Five membered ring heterocyclic 1,3,4-oxadiazoles, 1,3,4-thiadiazole and 1,2,4-triazoles and their derivatives are considered as an important class of compounds because of their diversified biological applications[1]. 1,3,4-oxadiazole derivatives showed antibacterial[2,3], anti-inflammatory[4], antitubercular[5], anticonvulsant[6], antimalarial[7] and antifungal agents[8].

1,3,4-thiadiazole exhibit various biological activities as anticancer[9], anticonvulsant[10],antibacterial[11],anti-inflammatory[12] and antifungicidal[13]. 1,2,4-triazole derivatives showed biological effects, such as antifungal[14], anticancer[15], antibacterial[16], anticonvulsant[17] and anti-inflammatory[18]. The synthesis of substituted 1,3,4-oxadiazoles was achieved by condensation of acyl hydrazine with acetic acid in phosphorous oxychloride to give 2,5-disubstituted 1,3,4-oxadiazole[19]. 2-Substituted 1,3,4-oxadiazole were synthesized from acid hydrazides by their reaction with carbon disulfide in ethanolic potassium hydroxide[20,21]. 1,3,4-oxadiazoles were synthesized by cyclization of substituted thiosemicarbazide by phosphoric acid[22], concentrated sulphuric acid[23] or methyl sulfonate[24]. 1,3,4-Thiadiazoles (I) and (II) were synthesized from substituted thiosemicarbazide by phosphoric acid[22] and concentrated sulphuric acid[25] respectively.

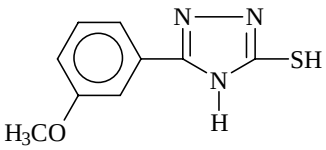


(I)

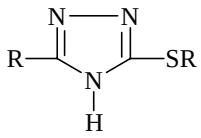


(II)

1,2,4-Triazole derivatives were synthesized from thiosemicarbazides by their reaction with sodium hydroxide solution as compound (III)[26]. 5-alkyl-1,2,4-triazole-3-thiol was treated with alkyl halides to give alkylthio derivative (IV)[27].



(III)



(IV)

Experimental

N-Benzoyl amino acid (1,2)[28]

A mixture of amino acid (glycine or alanine) (0.12 mole), benzoyl chloride (22.4 g,0.16 mole) and sodium carbonate (20 g) in water (200 ml) was refluxed for 6 hours, the mixture was cooled to room temperature and acidified with concentrated hydrochloric acid (pH=6) and left to stand over night. The precipitate was filtered off, washed with cold water and recrystallized from water. Compound(1), X=H, m.p. 111-112 ^{o}C; yield 80%, white crystals. IR,KBr υcm^{-1}, 1717(C=O), 2957(C-H aliphatic), 1070(C-O), 3418(N-H). Compound (2), X=CH_3; m.p. 116 ^{o}C; yield 85%; white crystals. IR,KBr υcm^{-1},1100(C-O),1686(C=O),3071(C-H aromatic), 3449(N-H),2900(C-H aliphatic).

2-phenyl-4-methyl/H-Δ^2-5-oxazolinone(3,4)[29]

Compound (1,2) (0.018 mole) was dissolved in acetic anhydride (15ml). The mixture was heated at 70 ^{o}C for 1 hour, after cooling ether-petroleum ether (10:50 ml) were added then the mixture stirred for 30 minutes. Compound (3) was isolated as oil, compound (4) as white solid was recrystallized from petroleum ether-ether (1:1). Compound (3); X=H, yellow oil, yield 55%, IR,KBr υcm^{-1}, 1755(C=O),1644(C=N), 2942 (C-H,aliphatic), 3025(C-H,aromatic), 1046, 1126(C-O). Compound (4); X=CH_3, m.p. 98 ^{o}C, yield 75%, IR, KBr υcm^{-1}, 1746(C=O), 1618(C=N), 3005 (C-H, aromatic),1050(C-O).

Acid Hydrazide (5,6)[29]

A mixture of compound (3or4)(0.035mole)in dioxane (10ml) and hydrazine hydrate (1.12 g, 0.035mole) was heated for 1 hour. The solvent was evaporated to give compound (5) as an oil whereas compound(6) was dissolved in ethanol and crystallized by water, filtered and dried. Compound (5); X=H, yield 62%,yellow oil.; IR,KBr υcm^{-1}, 1650(C=O), 3453(N-H). Compound (6); X=CH_3, m.p.260d., yield 75%, brown, IR,KBr υcm^{-1}, 1680(C=O),3056(C-H, aromatic),3311(N-H).

Substituted thiosemicarbazide (7,8)[29]

To acid hydrazides (5or6) (0.0025mole) in methanol(10ml), phenyl isothiocyanate (0.0025mole) in methanol (10ml)was added. The mixture

then refluxed for 2 hours. The solvent was evaporated under reduced pressure, compound (7) was recrystallized from ethanol. Compound (7); Ar=Ph, R=PhCO-NH, m.p.182-184 ^{o}C, yield 72%, pale green crystals; IR,KBr υcm^{-1}, 3444(N-H), 3009(C-H,aromatic), 2988(C-H,aliphtic), 1190(C=S),1645(C=O). Compound (8); Ar=4-$OCH_3C_6H_4$;R=PhCONH, yield 44%, green oil.; IR,KBr υcm^{-1}, 1663(C=O), 1115(C=S),3418(N-H).

5-Substiuted-4-aryl-1,2,4-triazole-3-thiol(9,10)[29]

A mixture of substituted thiosemicarbazide (7or8) (0.0014mole) in sodium hydroxide solution 1N (10ml) was heated at 80 ^{o}C for 1 hour, water (15 ml) then was added then acidified with dilute hydrochloric acid (pH=4.5). The precipitate was filtered off and recrystallized from ethanol. Compound (9); Ar=Ph ;R=RCONH, m.p. 195-197 ^{0}C, yield 75%, pale brown crystals.; IR, KBrυ cm^{-1}, 1630(C=N), 3452(N-H), 2940(C-H, aliphatic), 1122(C=S). Compound (10); Ar=4-$OCH_3C_6H_4$; R=RCONH, m.p.154 ^{o}C yield 81%, pale green crystals.; IR,KBr υcm^{-1}, 3451(N-H), 2910 (C-H,aliphatic), 1218(C=S), 1623(C=N).

2-Substituted-5-arylamino-1,2,4-triazole-3-thiol(11,12)[29]

Substituted thiosemicarbazide (7or8) was dissolved in concentrated sulphuric acid (1ml) then stirred at room temperature for 1 hour, cool water (25ml) was added, the precipitate was filtered,dried and recrystallized from ethanol. Compound (11); Ar=Ph; R=PhCONH, m.p.140-142 ^{o}C yield 71%, pale brown crystals.; IR,KBr υcm^{-1},3417 (N-H), 2983(C-H,aliphatic), 3122(C-H,aromatic), 1633(C=O), 1602(C=N), U.V. λmax 225nm. Compound (12); Ar=4-$OCH_3C_6H_4$; R=PhCONH, m.p. 222-224 ^{o}C yield 56%, pale brown.; IR, KBr υcm^{-1}, 3443(N-H), 1629 (C=O),1570(C=N).

2-Substituted-5-phenylamino-1,3,4-oxadiazole(13)[30]

A mixture of substituted thiosemicarbazide (7)(0.20 g,0.001mole) in methanol(25ml) and mercuric oxide (0.24g,0.001 mole) was refluxed for four hours, the mixture was filtered while hot, the solvent then evaporated under reduced pressure to give solid product, recrystallised from ethanol., m.p.135-137 ^{o}C d., yield 51%, brown crystals, IR, KBr υcm^{-1},3393(N-H), 3050(C-H,aromatic), 2852(C-H,aliphatic),1620(C=N),1088(C-O).

3,5-Disubstituted-1,2,4-triazole(14,15)[31]

1,2,4-triazole (9,10) (0.002mole) was dissolved in ethanol (20ml), the solution cooled in ice-bath, 4-carboxybenzaldehyde (0.002mole) was added, the mixture then kepted in ice-bath for 4-6 hours, the precipitate was filtered off, dried and recrystallized from ethanol-water. Compound (14); Ar=Ph; R=PhCONH, m.p.187-188 ^{o}C yield 81%, brown crystals.; IR,KBr υ cm^{-1},3305(O-H), 1294(C=S), 1612(C=N). Compound (15); Ar=4-OHC_6H_4 ;R=PhCONH, m.p.106 ^{o}C yield 61%, yellowish crystals.;

IR,KBr υcm^{-1}, 1599(C=N), 1156(C=S), 3300(OH), 2956 (C-H,aliphatic), 3165(C-H,aromatic).

Substituted thiosemicarbazide (16)[32]

A mixture of hydrazide (5)(1.48 g, 0.01mole), ammonium thiocyanate (2.28 g, 0.03mole) and concentrated hydrochloric acid (4ml) in ethanol (50 ml) was refluxed for 22 hours. The solvent was evaporated under reduced pressure to give oily product. yield 65%, colour pale violet IR, KBr υcm^{-1},3444(N-H),2950(C-H, aliphatic),1664(C=O),1044(C=S).

5-Substituted-1,2,4-triazole-3-thiol(17)[33]

A mixture of substituted thiosemicarbazide (16)(0.412 g,0.002mole) in 4% sodium hydroxide solution (25ml) was refluxed for three hours, the mixture was cooled acidified with 10% hydrochloric acid. The precipitate then filtered and recrystallized from ethanol-water., m.p. 200 ^{o}C d. ,yield 62%, pale green crystals, IR,KBr υcm^{-1}, 3419(N-H), 1635(C=N),3090 (C-H,aromatic), 2980(C-H,aliphatic), 1125(C=S).

3,5-Disubstituted-4-amino-1,2,4-triazole(18)[34]

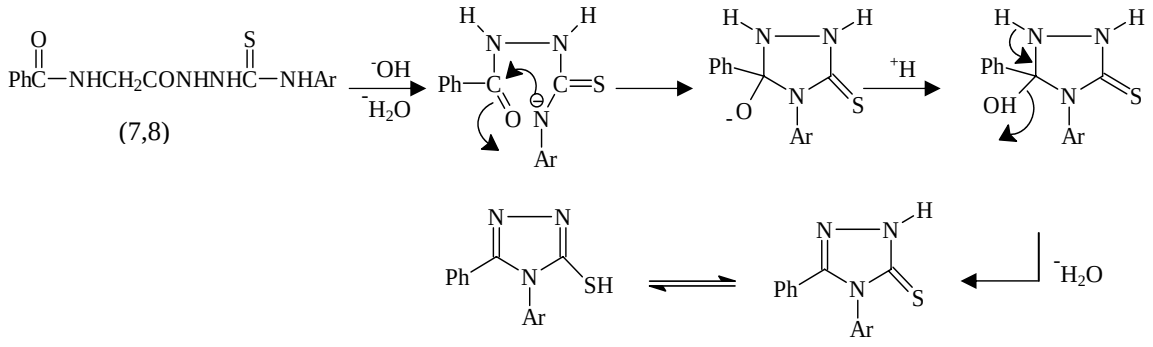
Acid hydrazide (6) (0.32g,.002 mole) was heated at 130-150 ^{o}C for 1 hour, water (50ml) was added then refluxed for 15 minutes. A solid product was formed on cooling. m.p. 240 ^{o}C d. pale brown crystals, yield 70% IR,KBr υcm^{-1}, 3318(N-H), 3058(C-H,aromatic), 2927(C-H, aliphatic), 1596 (C=N),1650(C=O).

Result and discussion

The synthesis of some substituted 1,3,4-oxadiazole,1,3,4-thiadiazoles and 1,2,4-triazoles is reported scheme-1-. Amino acid (glycine and alanine) was treated with benzoyl chloride to give N-benzoyl amino acids(1,2). IR spectra of compound (1) KBr cm^{-1} 3418(N-H), 2957 (C-H,aliphatic), 1717(C=O) and 1070(C-O), whereas compound (2) IR spectra showed absorption bands at cm^{-1} 3449 (N-H), 3071 (C-H,aromatic), 2900(C-H, aliphatic), 1686(C=O) and 1100(C-O). U.V. spectra λmax 234,205nm. Compound (1,2) were treated with acetic anhydride to give oxazolinones (3,4). The IR spectra of compounds (3,4) showed absorption bands within the range 3050-3025 cm^{-1} that were attributed to (C-H, aromatic), 1746-1755 cm^{-1} (C=O), 1634 cm^{-1}(C=N) 1050-1126 cm^{-1}. U.V. spectra λmax 217,242nm. Compounds 3,4 were converted into the acid hydrazides(5,6) by their reaction with hydrazine hydrate in dioxane. The IR spectra for compounds (5,6) showed an absorption band between 3311-3453cm^{-1}(N-H), 1650-1680cm^{-1}(C=O), U.V. spectra λmax 216,206nm. Acid hydrazide (5,6) were reacting with phenyl isothiocynate in methanol to give substituted thiosemicarbazide (7,8), IR spectra of compounds (7,8) showed absorption band at 3418-3444cm^{-1} due to (N-H) ,1645-1663 cm^{-1}(C=O),1115-1190 (C=S), U.V. spectra λmax (242,221nm). Substituted thiosemicarbazides (7,8) were treated with sodium hydroxide solution,

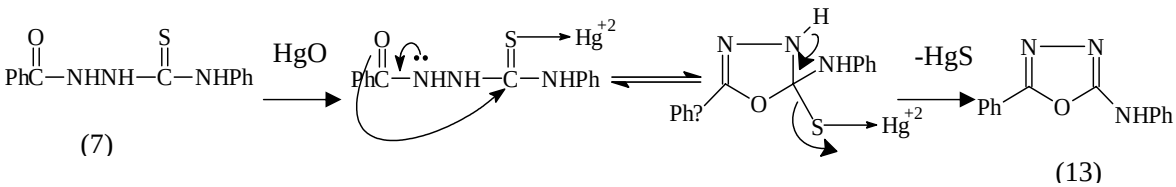
concentrated sulphuric acid to give 1,2,4-triazoles (9,10) and 1,3,4-thiadiazole (11,12) respectively. whereas treatment of compound (7) with mercuric oxide give 1,3,4-oxadiazole(13). The IR spectra of compounds (9,10) showed absorption band at 3451-3452cm^{-1}due to (N-H),1623-1630cm^{-1} (C=N),1122-1218 (C=S).U.V. spectra λmax (285,212 nm). IR spectra of compounds (11,12) the absorption band of (N-H) appeared at 3417-3443cm^{-1} (C=O) at 1629-1633 cm^{-1}, (C=N) at 1570-1602cm^{-1}. U.V.spectra λmax (225,200 nm).

The mechanism for the conversion of (7,8) to (9,10) as follows[35]:



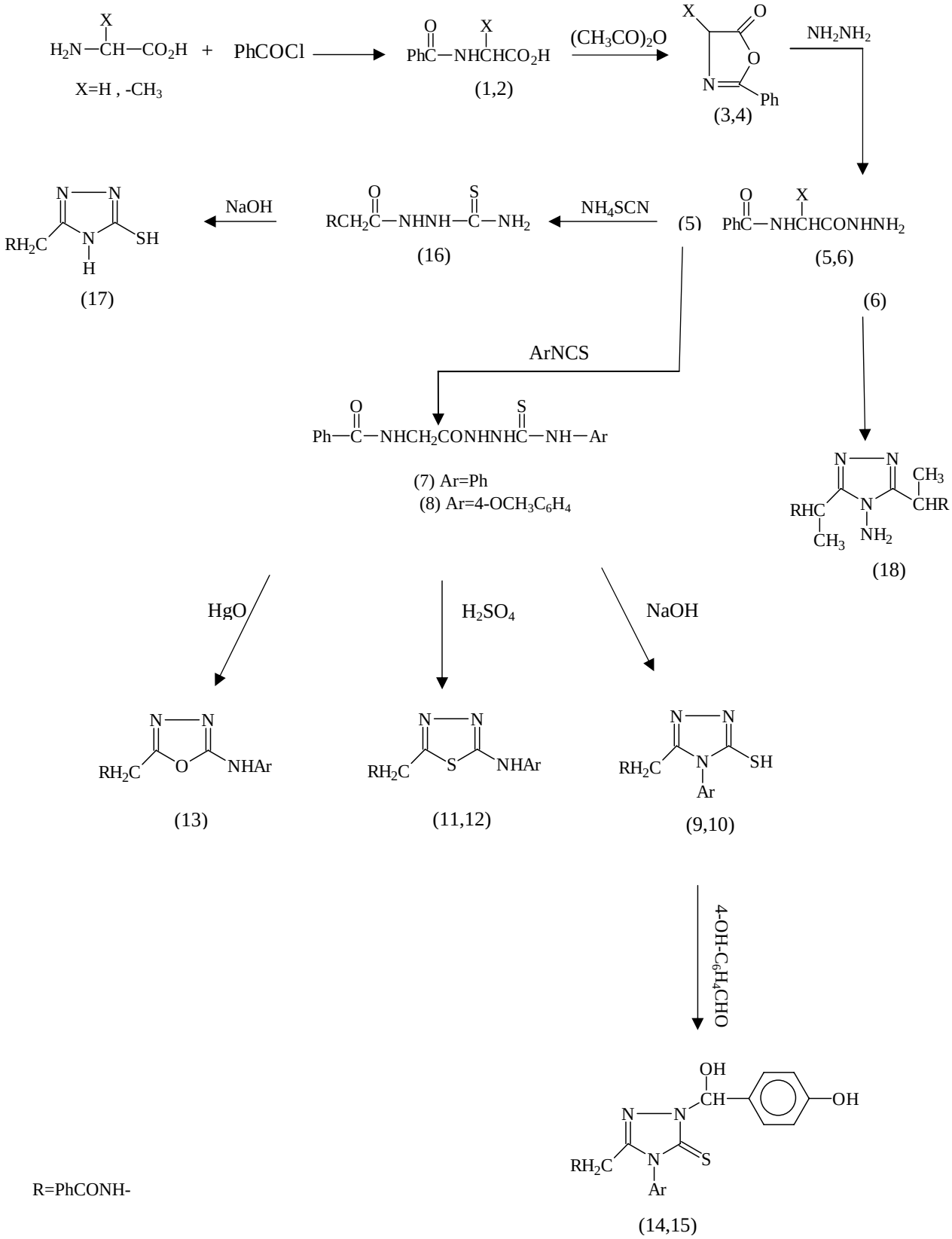
(7,8) (9,10)

The IR spectra of compound(13) showed absorption bands at 3393 cm^{-1} (N-H),3050 cm^{-1} (C-H, aromatic), 1620(C=N), 1088(C-O). U.V. spectra λmax 325nm. The proposed mechanism for the conversion of (7) to (13) as follows:



(7) (13)

The reaction of triazoles (9,10) with 4-hydroxybenzaldehyde gave substituted 1,2,4-triazoles(14,15). The IR spectra of of compounds (14,15) showed absorption bands at 3305-3300 (O-H), 1599-1612(C=N),1156-1294 (C=S). U.V. spectra λmax. 202,257nm. The reaction of acid hydrazide (5) with ammonium thiocyanate and hydrochloric acid in ethanol afforded substituted thiosemicarbazide (16) which cyclized to 1,2,4-triazole (17) by aqueous sodium hydroxide. The IR spectra of compound (16) showed absorption bands at 3444 cm^{-1} (N-H),1664 cm^{-1} (C=O), 1044 cm^{-1} (C=S). U.V. spectra λmax. 204nm. Whereas compound (17) the absorption band for (N-H) appeared at 3419cm^{-1}, for (C=N) at 1635 cm^{-1} and for (C=S)1125 cm^{-1}. U.V.spectra λmax. 212nm. Acid hydrazide (6) was converted into triazole (18) when heated at 130-150 ^{o}C for one hour. The IR spectra of compound (18) showed absorption band at 3318cm^{-1} (N-H),1630 cm^{-1}(C=O),1596cm^{-1} (C=N). U.V.spectra λmax. 203nm.


X=H , -CH3
(1,2)
(3,4)
(5)
(5,6)
(6)
(16)
(17)
(18)
(7) Ar=Ph
(8) Ar=4-OCH3C6H4
(13)
(11,12)
(9,10)
(14,15)
R=PhCONH-

Scheme-1-

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