Synthesis of Some New Heterocyclic Compounds Using α- (N-Saccharin) Acetohydrazide

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Abstract

Different new compounds derived from α- (N-saccharin) acetohydrazide (1) as starting material were synthesized. The Schiff bases (2a, b) were obtained by condensation of (1) with 2,4-dimethoxybenzaldehyde and *p*-dimethylaminobenzaldehyde, The cyclization of (2a, b) with maleic anhydride, phthalic anhydride, glycine, alanine and chloroacetyl chloride gave the corresponding oxazepine, (3,4a, b), imidazolidine (5a-d) and azitidine (6 a,b) derivatives. . Reaction (1) with ammonium thiocyanate gave triazol derivative (7). Compound (7) that cyclized either with chloroacetic acid in presence sodium acetate or a mixture of chloroacetic acid and 2,4-dimethoxybenzaldehyde or *p*-dimethylaminobenzaldehyde to give the corresponding derivatives (8) and (9 a,b). IR, elemental analysis, ^{1}HNMR and ^{13}C-NMR were used to characterize the target compounds

Keywords: α- (N-saccharin) acetohydrazide, oxazepine, imidazolidine, azitidine**,** triazol

الخلاصة

تم تحضير قواعد شف (2a,b) من تكاثف المركب الاساسي الفا– (N– سكرين) أسيتوهايدرازيد (1) مع 4,2– ثنائي ميثوكسي بنزالديهايد أو بارا– ثنائي مثيل أمينوبنزالديهايد. حضرت مشتقات الاوكسازيين (3,4 a,b) ومشتقات الاميدازولدين (5a–d) وكذلك مشتقات الازيتيدين (6a–b) من خلال الغلق الحلقي لقواعد شف (2a,b) مع حامض الماليك اللامائي وحامض الفثاليك اللامائي والكلايسين والالنين وكلوراستيل كلورايد على التوالي . تفاعل المركب (1) مع ثايوسينات الامونيوم أعطى مشتق الترايزول (7) . حضر المشتقان (8) و (9a,b) من الغلق الحلقي للمركب (7) مع كلورو حامض الخليك بوجود خلات الصوديوم او مزيج من كلورو حامض الخليك و 4,2– ثنائي ميثوكسي بنزالديهايد أو بارا– ثنائي مثيل أمينوبنزالديهايد. شخصت المركبات المحضره بواسطة طيف الأشعه تحت الحمراء والتحليل الدقيق للعناصر وطيف الرنين النووي المغناطيسي البروتوني (^{1}H–NMR) و ^{13}C–NMR

Introduction

Heterocyclic compounds are considered one of important types of organic compounds due to their implication in drugs and industrial studies [1-5]. The design of new prepared compounds based on structurally containing other biologically active heterocycles or side chains reported in the field of cancer therapy such as triazoles [6, 7] Schiff bases [8,9] or in the field of antibiotics such as oxazepines [10] azetidines [11-14] and imidazolidins [15] . The *B*-lactam ring is part of core structure of several families, the principal ones being the penicillins,cephalosporins,carbapenems and monolactams,which are,therefor,also called *B*- lactam antibiotics[16] .Today,thousands of chiral compounds containing *B*-lactam rings are known. Whether isolated from natural sources or chemically synthesized, they are marked by high efficacy and safe toxicological profiles[17] . The triazol compounds possess fungicidal and plant growth regulation activity. The substituted triazole nucleas is particularly common, and can be found in marketed drugs such as fluconozole , terconazole and rizatriptan alperazolam[18] .

Experiment

Melting points were recorder using electrothermal melting point apparatus and were uncorrected. FTIR spectra were run on a Shimadzu FTIR-8400S spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorder on Bruker Ultra Shield, 300MHz, using DMSO-d_6 as solvent and TMS as internal standard.Elemental analysis was run by Eurovectro, EA 3000 A, ITALY. Thin-layer chromatography was performed glass plats coated with 0.25 mm layer of silica-gel (Fluka).

Preparation of Schiff Bases Derivatives (2a,b)

General procedure: A mixture of compound (1) (0.7 gm, 2.7 mmol.), appropriate aromatic aldehyde namely 2,4-dimethoxybenzaldehyd *p*- dimethylaminobenzaldehyde (2.7mmol.) in(15ml) ethanol was refluxed for 3 h. The formed precipitate after cooling was filtered, dried and recrystallized from benzene and ethanol (1:1) to give compounds (2a,b) respectively.

N-(2,4-Dimethoxybenzylidene)-α- (N-saccharin) acetamide (2a)

Yield 46%, m.p. 50-52°C, R_f (0.179), IR (KBr) cm^{-1}: 3300(NH), 1697 (C=O amide), 1653(C=N). Anal. Calcd. C, 53.59; H, 3.97; N, 10.42. Found: C, 53.40; H, 3.78; N, 10.36. ^{1}H-NMR (DMSO-d_6)δ: 3.4(s, 6H, 2(OCH_3)), 4.6(s, 2H, N-CH_2-), 7.1-8.3(m, 7H, Ar-H),8.8(s, 1H, =CH), 10.2(s, 1H, NH).

/N-(*p*-Dimethylaminobenzylidene)-α-(N-saccharin)acetamide (2b)

Yield 47%, m.p. 166-168°C, R_f (0.077), IR (KBr) cm^{-1}: 3300(NH), 1169 (C=O amide), 1650(C=N). Anal. Calcd. : C, 55.95; H, 4.66; N, 14.51. Found: C, 54.98; H, 4.54; N, 13.86. ^{1}H-NMR (DMSO-d_6)δ: 3.2(s, 6H, $(NCH_3)_2$), 4.2 (s, 2H, N-CH_2-), 7.0-7.8(m, 8H, Ar-H), 8.7(s, 1H, C=CH), 10.1(s, 1H, NH).

Preparation of Oxazepines Derivatives (3, 4 a, b)

General procedure: A mixture of compounds 2a or 2b (1.1 mmol.) and the appropriate acid anhydride namely maleic anhydride or phthalic anhydride (1.1 mmol.) in (20 ml) T.H.F. was refluxed for 24h. The formed precipitate

was filtered, dried and recrystlaized from benzene and ethanol (2:1) to give compounds (3, 4 a, b) respectively.

2-(2,4-Dimetoxyphenyl)-3-[α-(N-saccharin)acetamido]-2,3-dihydro-1,3-oxazepine- 4-7-dione (3a)

Yield 67%, m.p. 128-130°C, R_f (0.839), IR (KBr) cm^{-1}: 3200(NH), 1720,1775(C=O oxazepine ring), 1664(C=O amide),^{1}H-NMR (DMSO-d_6) δ 3.8 (s, 6H, 2(OCH_3)), 4.3(s,2H, NCH_2), 6.9-8.0(m, 9H, Ar-H, CH=CH), 9.1(s, 1H, C-H oxazepine ring), 10.0 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6) δ: 50(O-CH_3), 63(N-CH_2-), 80,133 (CH, C=C oxazepine ring),140-150(CH aromatic), 165,168 (C=O oxazepine ring, amide).

2-(*p*-Dimethylaminophenyl)-3-[α-(N-saccharin)acetamido]-2,3-dihydro-1,3-oxazepine-4,7-dione (3b)

Yield 63%, m.p. 63-65°C, R_f (0.871), IR (KBr) cm^{-1}: 3263(NH), 1720,1789(C=O oxazepine ring), 1662(C=O amide),^{1}H-NMR (DMSO-d_6) δ: 3.2(s, 6H, N(CH_3)$_2$), 4(2H N-CH_2-,), 6.8-7.9(m, 10H, Ar-H, CH=CH), 8.9(s, 1H, C-H oxazepine ring), 10.2 (s,1H,NH). ^{13}C-NMR (DMSO-d_6)δ:45(N(CH_3)$_2$),63(N-CH_2), 80,133 (CH,C=C oxazepine ring), 140-150 (CHaromatic),165,168(C=O) (oxazepine ring, amide).

2-(2,4-Dimethoxyphenyl)-3-[α-(N-saccharin)acetamido]-2,3-dihydro-benzo[e]-1,3-oxazepine-4-7-dione (4a)

Yield 37%, m.p. 130°C d., R_f (0.824), IR (KBr) cm^{-1}: 3300(NH), 1730,1680 (C=O oxazepine ring), 1620(C=O amide), ^{1}H-NMR (DMSO-d_6) δ:3.6(s,6H,2(OCH_3),4.3(s,2H,NCH_2),7.0-8.2(m,11H,Ar-H),9.1(s,1H,C-H oxazepinering), ^{13}C-NMR(DMSO-d_6)δ 50 (O-CH_3), 65 (N-CH_2-), 80,133(CH,C=Coxazepine ring), 130-150 (CHaromatic), 165,168(C=O) (oxazep ine ring, amide).

2-(*p*-Dimethylaminophenyl)-3-[α-(N-saccharin)acetamido]-2,3-dihydro-benzo[e]-1,3-oxazepine-4,7-dione (4b)

Yield 63%, m.p. 125°C d., R_f (0.794), IR (KBr) cm^{-1}: 3290(NH), 1720,1690 (C=O oxazepine ring), ^{1}H-NMR(DMSO-d_6) δ:3.3(s, 6H, (N(CH_3)$_2$), 4.3(s, 2H, N-CH_2), 7.0-8.2(m, 12H, Ar-H), 9.0(s, 1H, CH oxazepine ring),10.0(s,1H, NH). ^{13}C-NMR(DMSO-d_6) δ:45(N(CH_3)$_2$), 63(N-CH_2), 80,133(CH,C=C oxazepine ring), 140-150 (CHaromatic) ,165,168 (C=O) (oxazepine ring, amide).

Preparation of Imidazolidine derivatives (5a-d)

General procedure: A mixture of compounds 2a or 2b (4.9 mmol.) and appropriate α-amino acid namely glycine or alanine (4.9 mmol.) in (15 ml) T.H.F. was refluxed for 24h. The mixture was poured into ice water. The precipitate obtained was filtered and recrystallized from ethanol and T.H.F (1:3) to give compounds (5a-d) respectively.

2-(2,4-Dimethoxy phenyl)-3-[α-(N-saccharin)acetamido] imidazolidine-4-one (5a)

Yield 45%, m.p. 185-187°C, R_f (0.500), IR (KBr) cm^{-1}: 3400(NH), 1720 (C=O cyclic), 1640(C=O amide). Anal. Calcd.: C, 52.17; H, 4.34; N, 12.7. Found: C, 51-83; H, 4.17; N, 11.82, ^{1}H-NMR (DMSO-d_6) δ: 2.9(s,1H, NH cyclic), 3.9 (s, 6H, 2(OCH_3)), 4.2(s, 2H, N-

CH_2),6.7(s, 2H,CH_2-cyclic),7.2-7.8(m,7H,Ar-H), 8.2 (s, 1H CH cyclic), 8.7(s,1H, NH).

2-(*p*-Dimethylaminophenyl)-3-[α-(N-saccharin)acetamido] imidazolidine-4-one (5b)

Yield 60%, m.p. 185-187°C, R_f (0.200), IR (KBr) cm^{-1}: 3440(NH), 1745 (C=O cyclic), 1640(C=O amide). Anal. Calcd.: C, 54.17; H, 4.74; N, 15.80. Found: C, 54.02; H, 4.23; N, 15.14, ^{1}H-NMR (DMSO-d_6) δ: 3.0(s,1H, NH cyclic), 3.4(s, 6H, $N(CH_3)_2$), 4.3(s, 2H, N-CH_2-), 6.5(s, 2H, CH_2-cyclic), 7.0-7.7(m, 8H, Ar-H), 8.0(s, 1H, CH cyclic), 8.7(s, 1H, NH).

5-Methyl-2-(2,4-dimethoxyphenyl)-3-[α-(N-saccharin)acetamido]imidazolidine-4-one(5c)

Yield 43%, m.p. 121-123°C, R_f (0.368), IR (KBr) cm^{-1}: 3400(NH), 1720(C=O cyclic), 1640(C=O amide). Anal. Calcd.: C, 53.16; H, 4.64; N, 11.81. Found: C, 53.02; H, 4.48; N, 10.87, ^{1}H-NMR (DMSO-d_6) δ: 1.5 (d, 3H, CH_3), 3.0(s,1H, NH cyclic), 4.0 (s, 6H, 2(OCH_3)), 4.2(s, 2H, N-CH_2-), 6.7(q, 1H, CH-cyclic), 7.2-7.8(m, 7H, Ar-H), 8.4(s,1H, CH-Ar), 9.0(s,1H, NH).

5-Methyl-2-(p-dimethylaminophenyl)-3-[α-(N-saccharin)acetamido] imidazolidine-4-one (5d)

Yield 56%, m.p. 190°C dec., R_f (0.286), IR (KBr) cm^{-1}: 3380(NH), 1724 (C=O cyclic), 1660(C=O amide). Anal. Calcd.: C, 53.96; H, 3.64; N, 14.98. Found: C, 52.90; H, 3.01; N, 13.95, ^{1}H-NMR (DMSO-d_6) δ: 1.4(d, 3H, CH_3), 3.0(s,1H, NH cyclic), 3.6(s, 6H, $N(CH_3)_2$), 4.0(s, 2H, N-CH_2-), 6.7(q, 1H, CH-cyclic),7.0-7.8(m,8H,Ar-H), 8.0(s, 1H, CH-Ar), 8.8(s, 1H, NH).

Preparation of Azetidinone Derivatives (6a,b)

General procedure: A solution of chloroaacetyl chloride (0.8 mmol.) in dry methylene chloride (10 ml) was slowly added to a solution of Schiff base 2a or 2b (0.5 mmol.) and triethylamine (1.0 mmol.) in (10 ml) methylene chloride at 0 to 5 °C. The reaction mixture was then allowed to warm to room temperature and stirred for 15 h. The mixture was poured into ice water. The precipitate obtained was filtered and recrystallized from hexane and ethylacetate to give compounds (6 a,b) respectively.

3-Chloro-4-(2,4-dimethoxyphenyl)-1-[α-(N-saccharin)acetamido]azitidine-2-one (6a)

Yield 80%, m.p. 150-153°C, R_f (0.629), IR (KBr) cm^{-1}: 3410(NH), 1770 (C=O lactm ring), 1620(C=O amide). Anal. Calcd.: C, 50.10; H, 3.75; N, 8.76. Found: C, 49.75; H, 3.61; N, 7.38, ^{1}H-NMR (DMSO-d_6) δ:4.0(s, 6H, 2(OCH_3), 4.3(s, 2H,N-CH_2-), 5.0(d, 1H,-CH-Cl),7.0-7.6(m, 7H, Ar-H), 7.9(d, 1H,CH-Ar), 8.9(s,1H, NH).

3-Chloro-2-(*p*-dimethylaminophenyl)-1-[α-(N-saccharin)acetamido]azitidine-2-one (6b)

Yield 75%, m.p. 230-232°C, R_f (0.657), IR (KBr) cm^{-1}: 3470(NH), 1770 (C=O lactm ring), 1650(C=O amide). Anal. Calcd.: C, 51.94; H, 4.11; N, 12.12. Found: C, 51.39; H, 3.72; N, 11.78, ^{1}H-NMR (DMSO-d_6) δ:3.4 (s, 6H, $N(CH_3)_2$), 4.3(s, 2H, N-CH_2-), 5.0(d,1H,-CH-Cl), 7.0-7.6(m, 8H, Ar-H), 7.9(d, 1H, CH-Ar), 8.8 (s, 1H, NH).

Preparation of 3-(N-methylsaccharin)-5-mercapto-1-H-1,2,4-triazole (7)

A mixture of compound (1) (0.69 gm, 2 mmol.) and ammonium thiocyante (0.89 gm, 12 mmol.) was fused at 200 °C for 30 min. The solid mass was triturated with hot water, cold and acidified with concentrated hydrochloric acid. The formed precipitate was filtered and recrystallized from ethanol to give compound (7).

Yield 65%, m.p. 195-197°C, R_f (0.867), IR (KBr) cm^{-1}: 3400(NH), 2599(SH), 1589 (C=N). ^{1}H-NMR (DMSO-d_6) δ: 4.9(s, 2H, NCH_2),6.9-7.5(m, 4H, Ar-H), 11.5 (s,1H,NH-cyclic. ^{13}C-NMR (DMSO-d_6) δ: 56(N-CH_2-), 120-130(C-H aromatic), 140 (C-SH), 148(C-triazol ring).

Preparation of 2-(N-methylsaccharine)-5-oxo-5,6-dihydrothiazolo[3,2-b]-1,2,4-triazol (8)

A mixture of compound (10) (0.2 gm, 1.0mmol.), chloroacetic acid (0.318 gm,1.0 mmol.) and anhydrous sodium acetate (0.17 gm, 2 mmol) in (10 ml) glacial acetic acid and (5 ml)acetic anhydride was refluxed for 6h. After cooling the reaction mixture was filtered, dried and recrystallized from ethanol to give compound (8).

Yield 72%, m.p. 165-167°C, R_f (0.933), IR (KBr) cm^{-1}: 1740 (C=O thiazol ring), 1850 (C=N). ^{1}H-NMR (DMSO-d_6) δ: 4.0(s, 2H, CH_2-cyclic), 5.1(s, 2H, N-CH_2-), 6.9-7.3(m, 4H, Ar-H). ^{13}C-NMR (DMSO-d_6) δ: 30(CH_2-cyclic), 60(CH_2-N), 120-130 (CH_2-aromatic), 185(C=O cyclic).

Preparation of Compounds (9a,b)

General procedure: A mixture of compound (10) (0.11 gm, 0.37 mmol.), chloroacetic acid (0.04 gm, 3.7 mmol.), anhydrous sodium acetate (0.06 gm, 7.4 mmol.) and appropriate aromatic aldehyde, namely 2,4-dimethoxy benzaldehyde and *p*-dimethylaminobenzaldehyde (0.37 mmol) in(5 ml) glacial acetic acid and (3 ml) acetic anhydride was refluxed for 6h. after cooling, the reaction mixture was filtered, dried and recrystallized from ethanol to give compounds (9a,b) respectively.

2-(N-methylsaccharin)-6-(2,4-dimethoxybenzylidene)-5-oxo-5-hydro thiazolo[3,2-b]-1,2,4-triazol (9a)

Yield 59%, m.p. 157-159°C, R_f (0.167), IR (KBr) cm^{-1}: 1745 (C=O thiazol ring), 1590 (C=N), 1530 (C=C). Anala. Calcd.: C, 52.06; H, 3.3; N, 11.57. Found: C, 51.27; H, 3.07; N, 11.12. ^{1}H-NMR (DMSO-d_6) δ: 3.5(s, 6H, 2(OCH_3)), 5.0(s, 2H, N-CH_2-), 6.2(s, 1H,=CH), 7.5-8.2(m, 7H, Ar-H).

2-(N-methylsaccharin)-6-(*p*-dimethylaminobenzylidene)-5-oxo-5-hydrothiazolo [3,2-b]-1,2,4-triazol (9b)

Yield 63%, m.p. 168-170°C, R_f (0.233), IR (KBr) cm^{-1}: 1750(C=O thiazol ring), 1590 (C=N), 1510 (C=C). Anala. Calcd.: C, 53.96; H, 3.64; N, 14.98. Found: C, 53.61; H, 3.37; N, 14.49. ^{1}H-NMR (DMSO-d_6) δ: 3.2(s, 6H, 2N(CH_3)), 5.0(s, 2H, N-CH_2-), 6.0 (s, 1H,=CH), 7.5-8.2(m, 8H, Ar-H).

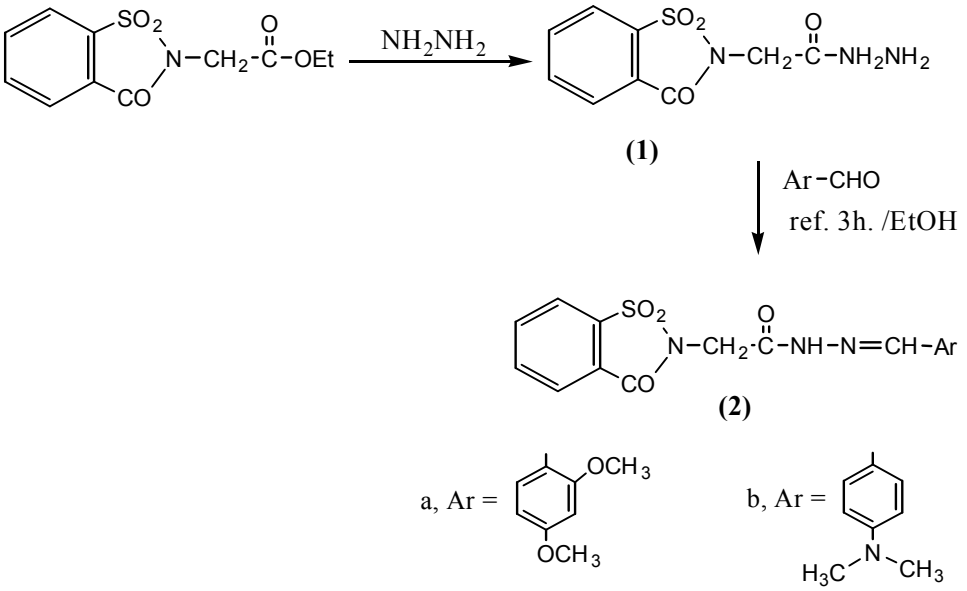
Results and Discussion

α- (N-saccharinacetohydrazide (1) was chosen as the starting material for the synthesis of all derivatives (2-9). Schiff-base (2a, b) (scheme 1) were prepared by condensation of (1) with the aromatic aldehydes namely 2, 4-dimthoxybenzaldehyde and *p*-dimethylaminobenzaldehyde ,in refluxing ethanol. The I.R. and ^{1}HNMR spectrum of formed Schiff bases showed

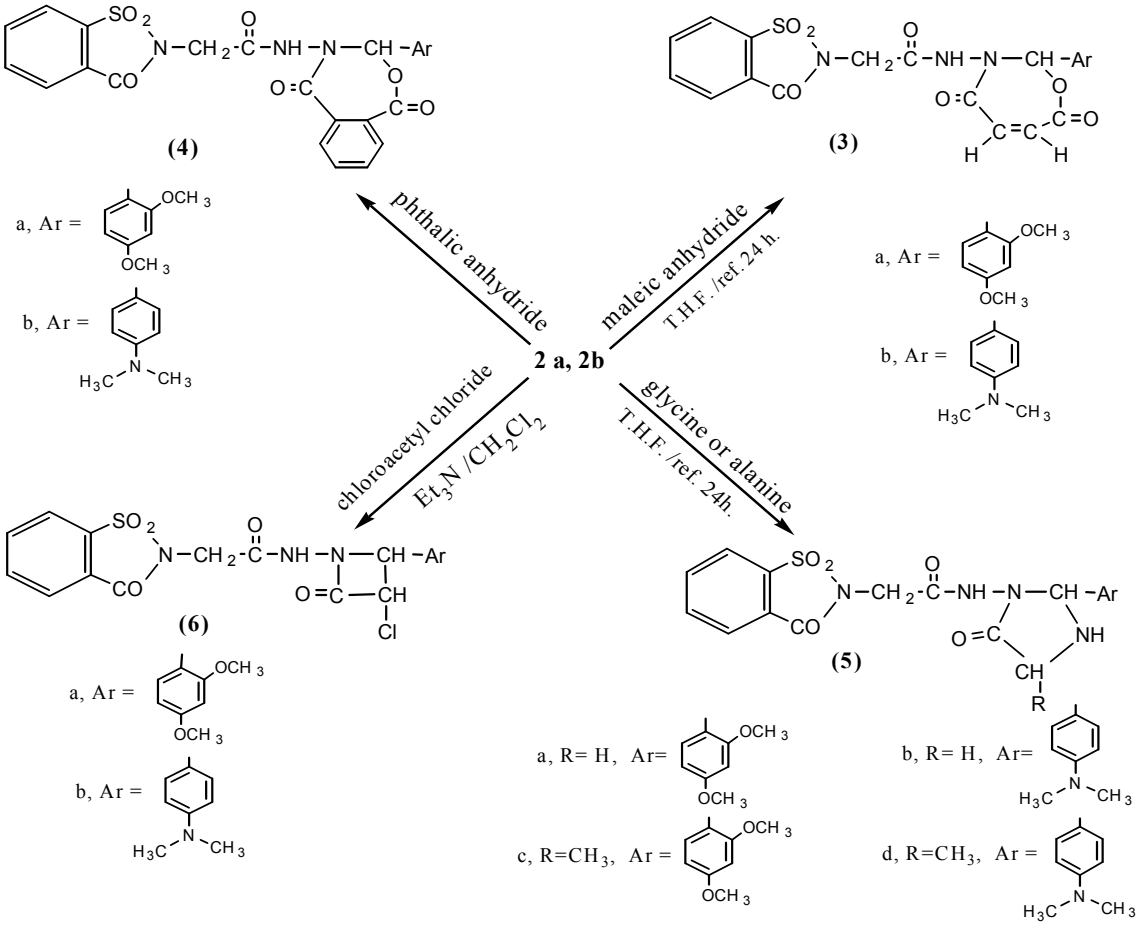
the presence of C=N band at 1620-1650 cm^{-1} and a singlet signal for azomethine (CH=N) at 8.7-8.8 ppm. Cyclization of (2a, b) with phthalic anhydride and maleic anhydride gave the corresponding oxazepine derivatives (3, 4a, b) (scheme 2). The oxazepine rings proton apper singlet signal at 8.9-9.1 ppm, while the ^{13}C-NMR spectrum of these derivatives showed the following signals due to oxazepine ring: (80) CH, (133) C=C and(165) C=O. Also cyclization of (2a,b) with α-amino acids such as glycine and alanine afforded the corresponding imidazolidine derivatives(5a-d) (scheme 2) The I.R. and ^{1}H-NMR spectrum of these derivatives showed presence of carbonyl group of imidazolidine ring at 1720-1745 cm^{-1} and a singlet signal at 8-8.4 ppm due to (CH) proton for imidazolidine ring Monocyclic *β*-lactams (6a,b) (scheme 2) were prepared by the reaction of imines (2a,b) with chloroacetyl chloride in dry methylene chloride in the presence of trimethyl amine via a [2+2] cyclo addition reaction [20]. The I.R. spectrum of formed azetidineones showed the presence of *β*-lactam carbonyl absorption at 1770 cm^{-1} while the ^{1}H-NMR spectrum showed two doublet signals at 7.9 ppm and 5.0 ppm assigned to (CH) protons of β-lactam ring at positions 3 and 4 respectively.

Moreover, fusion of (1) with ammonium thiocyanate at 200 °C for 30 min. gave the triazole derivative (7) which cyclized with chloroacetic acid in presence of sodium acetate to give compound (8).

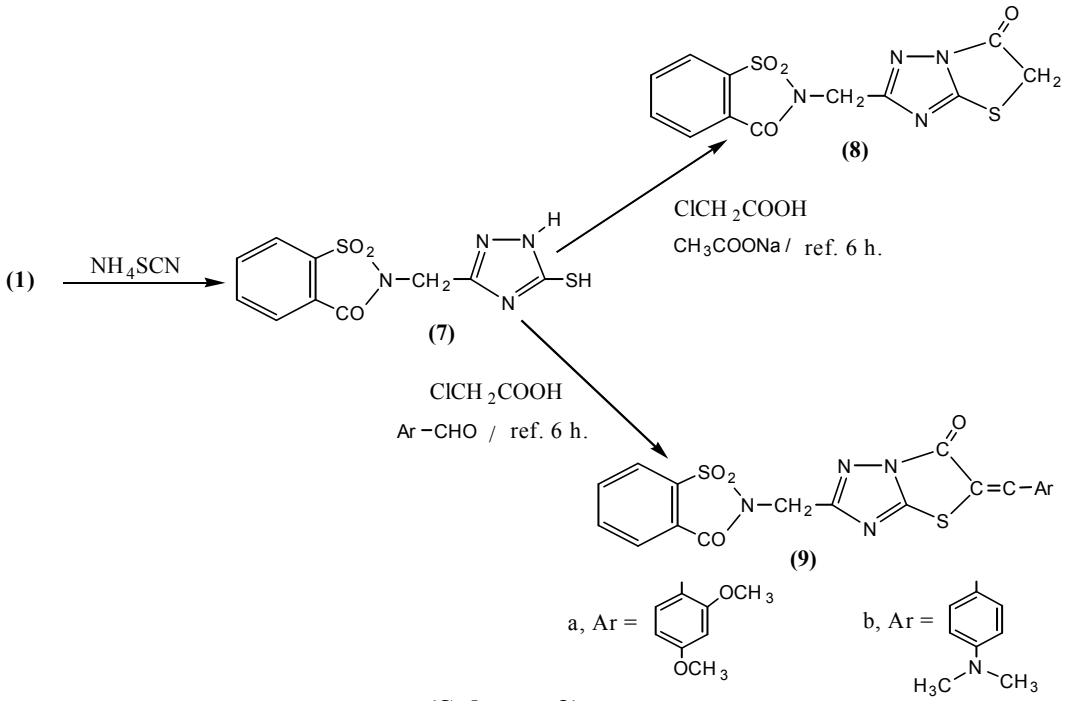
Moreover, the compound (7) that cyclized with a mixture of chloroacetic acid and aromatic aldehyde namely 2, 4-dimethoxybenzaldehyde and *p*-dimethylamino benzaldehyde to give the corresponding thiazolotriazole derivatives (9a, b) according to reported method [17] (scheme 3). The ^{1}H-NMR spectrum of 8 and 9 showed a singlet signal at 4 and 6-6.2 ppm due to CH_2-cyclic and =CH respectively



(Scheme 1)



(Scheme 2)



(Scheme 3)

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