Turkish Journal of Chemistry

Volume 32 | Number 2 Article 10

1-1-2008

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Turk J Chem
32 (2008) , 229 – 235.

Synthesis and Characterization of Novel Azole Heterocycles Based on 2,5-Disubstituted Thiadiazole

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Received 15.08.2007

Starting from 2-amino-5-mercapto-1,3,4-thiadiazole (**1**), a variety of new 1,2,4-triazino[5,4-b][1,3,4] thiadiazole (**3**), pyrazole (**4**), [1,2,4]triazolo[3,4-b] [1,3,4]thiadiazole (**5**), phthalazine-3,6-dione (**6**), azo derivatives (**9**), pyrimidine -2,4,6-trione (**11**), Schiff base (**12**) and pyrrolidine (**13**) derivatives have been synthesized. All proposed structures were supported by FT-IR, ^{1}H-NMR, ^{13}C-NMR elemental analysis, and MS spectroscopic data.

Key Words: 1,3,4-thidiazoles, fused heterocyclic ring, Schiff bases.

Introduction

The development of simple synthetic routes to widely used organic compounds using readily available reagents is one of the main objectives of organic synthesis. Nitrogen heterocycles are of a special interest because they constitute an important class of natural and nonnatural products, many of which exhibit useful biological activities. One-pot efficient synthesis of heterocyclic derivatives may permit the development of novel therapies for the treatment of epilepsy, pain and other neurodegenerative disorders.

Pyrazoles have attracted much attention recently as their synthesis is more accessible and their diverse properties are appreciated. One of the most important pyrazole activities are the effective antirheumatoidal (SC-58635 Celecoxib) and antiviral agents (Pyrazomycin), hormone oxytocin agonists (WAY-VNA-932), and selective Human C1s inhibitors.[1]

1,2,4-Triazole and its derivatives are found to be associated with various biological activities.[2] For example, Fluconazole is used as an antimicrobial drug, while Vorozole, Letrozole, and Anastrozole are nonsteroidal used for treatment of cancer and Loreclezole is used as an anticonvulsant.[3] Also, the synthesis of triazoles fused to another heterocyclic ring, especially those in which triazoles fused to thiadiazoles, has attracted particular attention due to their diverse applications.[4]

Some Schiff bases bearing aryl groups or heterocyclic residues possess excellent biological activities, which has attracted many researchers' attention in recent year.[5] They have been reported to be used as analgesic, anthelmintic, antitubercular, plant growth regulator, antiviral, antifungal, and anticancer.[6]

There has been considerable interest in the development of preparative methods for the production of pyrimidines. This seems to be because pyrimidines represent one of the most active classes of compounds, possessing a wide spectrum of biological activities, e.g., significant in vitro activity against unrelated DNA and RNA viruses, such as diuretic, anti-HIV, and cardiovascular activities.[7]

Phthalazine derivatives, like the other members of the benzodiazine series, have been widely applied as therapeutic agents due to their anticonvulsant, cardiotonic, vasorelaxant, and antiinflammatory properties.[8]

The occurrence of the pyrrole nucleus in many natural and synthetic biologically active compounds continues to contribute to the development of new synthetic methodologies toward this important heterocycle.[9]

Various 1,2,4-triazines and its derivatives are well known to possess an array of physiological activities, such as anticancer, muscle relaxant, hypnotic, anti-inflammatory, diuretic, and antihypertensive activities, and are widely used in pharmaceuticals.[10] Promoted by these observations, we aimed to obtain new derivatives of the above mentioned heterocyclic rings.

Experimental

General

Melting points were determined on Gallenkamp melting point apparatus and were uncorrected. The IR spectra of the compounds were recorded on a Shimadzu FTIR-8300 spectrometer as KBr disc; results are given in cm^{-1}. ^{1}H-NMR and ^{13}C-NMR spectra were recorded at 200.13 and 50.32 MHz, respectively, in DMSO-d_6, except for compound **11** in $CDCl_3$, on a Bruker Avance DPX-200 NMR spectrometer. The chemical shifts are reported in part per million (ppm) downfield from internal tetramethylsilane (TMS) (chemical shift in δ values). Electron impact MS spectra were obtained on a Shimadzu QP 1000 instrument at 70 eV. Elemental analyses were run using a Perkin-Elmer RE 2400 CHN analyzer. ^{1}H-, ^{13}C-NMR**,** elemental analysis, and Mass spectra were performed at Drug and Natural Product Department, University of Vienna, Australia.

Synthesis of 2-amino-5-mercapto -1,3,4-thiadiazole (1)

Prepared from thiosemicarbazide according to Katritzy et al. method as yellow crystals; M.P. 225-226 °C [Lit.[11] 227 °C]

Synthesis of 2-amino-5-hydrazino-1,3,4-thiadiazole (2)

Hydrazine hydrate (0.02 mol) was added to a solution of 2-amino-5-mercapto-1,3,4-thiadiazole (**1**) (0.01 mol) in abs. ethanol (15 ml) and the resulting mixture was refluxed for 6 h, or until the evolution of H_2S ceased. The solid that separated on cooling was filtered off and dried. M.P. 242-244 °C, Yield 70%. IR: 3400-3250($NHNH_2$), 3200, 3168(NH_2), 1600(C=N), 688(C-S). ^{1}H-NMR (DMSO-d_6)δ: 5.27(s, 2H, NH_2) (D_2O exchange, disappear), 6.00(s, 1H, NH) (D_2O exchange, disappear), 7.08(s, 2H, NH_2) (D_2O exchange, disappear). ^{13}C-NMR (DMSO-d_6)δ: 154.7, 161.5 (thiadiazole carbons).

Synthesis of 2-amino-4-(*p*-bromophenyl)-6H-1,2,4-triazino[5,4-b][1,3,4] thiadiazole (3)

A mixture of compound **2** (0.024 mol) with *p*-bromophenacyl bromide (0.024 mol) was heated under reflux for 5 h in abs. ethanol (30 ml). The solid product precipitate that separated upon cooling was filtered off and

recrystallized from chloroform. M.P. 180-182 °C, Yield 65%. IR: 3310-3150 (NH_2, NH), 3100(CH aromatic), 827(aromatic *p*-substituted). ^{1}H-NMR (DMSO-d_6)δ: 4.78(s, 2H, NH_2) (D_2O exchange, disappear), 7.34(s, 1H, NH triazine) (D_2O exchange, disappear), 7.73-7.95(m, 5H, Ar-H and =CH-). ^{13}C-NMR (DMSO-d_6) δ: 94.3, 94.8(triazine carbons), 127.9, 130.5, 132.3, 134.2(aromatic carbons), 168.3, 169.9 (thiadiazole carbons). MS: m/z = 309, 229, 157, 152, 129, 77.

Synthesis of 2-amino-5-(3,5-dimethyl-1H-pyrazole-1-yl)-1,3,4-thiadiazole (4)

Acetyl acetone (0.01 mol) was added to a solution of compound **2** (0.01 mol) in abs. ethanol (20 ml) and the reaction mixture was refluxed for 10 h. After concentration and cooling, the solid product formed was filtered off and recrystallized from benzene. M.P. 150-152 °C, Yield 77%. IR: 3300, 3250(NH_2), 3078(=CH-), 2977, 2850(CH aliphatic). ^{1}H-NMR (DMSO-d_6)δ: 3.32, 3.48(s, 3H, CH_3), 6.01(s, 1H, =CH-), 7.08(s, 2H, NH_2) (D_2O exchange, disappear). ^{13}C-NMR (DMSO-d_6)δ: 17.6(1C, CH_3), 52.1, 56.4(2C, <u>C</u>-CH_3), 96.6(1C, =CH-), 152.1, 163.2(thiadiazole carbons).

Synthesis of 2-amino-4-mercapto[1,2,4]triazolo[3,4-b][1,3,4] thiadiazole (5)

To a warmed ethanolic sodium hydroxide solution prepared by dissolving sodium hydroxide (0.01 mol) in abs. ethanol (30 ml), (0.01 mol) of compound **2** and (0.02 mol) of CS_2 were added. The mixture was refluxed in a water bath at 80 °C for 10 h, then allowed to cool to room temperature, poured into water, neutralized by dilute acetic acid, and the precipitate formed was filtered off and dried. M.P. 105-107 °C, Yield 65%. IR: 3250, 3200(NH_2), 2630(SH), 1665(C=N), 1380(C=S). ^{13}C-NMR (DMSO-d_6)δ: 96.2(1C, -N=<u>C</u>-), 155.8, 157.3(thiadiazole carbons). Anal. Calcd for $C_3H_3N_5S_2$: C,20.81; H,1.73; N,40.46. Found: C,21.03; H,1.89; N,40.55. MS: m/z = 173, 172, 159, 128, 99, 84, 66, 52.

Synthesis of 2-amino-5-(1,2-dihydrophthalizin-3,6-dione-1-yl)-1,3,4-thiadiazole (6)

Equimolar amounts of 2-amino-5-hydrazino-1,3,4-thiadiazole (**2**) (0.015 mol) and phthalic anhydride (0.015 mol) were dissolved in acetic acid (30 ml) and left under reflux for 10 h. Then the reaction mixture was poured on crushed ice, the formed crystals was collected by filtration, air died and recrystallized from chloroform. M.P. 198-200 °C, Yield 80%. IR: 3310-3200(NH_2, NH), 3080(CH aromatic), 1700 (C=O), 755(aromatic *o*-substituted). ^{1}H-NMR (DMSO-d_6)δ: 4.55(s, 2H, NH_2) (D_2O exchange, disappear), 7.96-8.00(m, 4H, Ar-H), 9.67(s, 1H, NH phthalazine) (D_2O exchange, disappear). ^{13}C-NMR (DMSO-d_6) δ: 124.3, 126.4, 128.7, 130.9(aromatic carbons), 162.243, 163.950 (thiadiazole carbons), 184.0, 186.0(2C, C=O).

Synthesis of 5-mercapto-2-(3-hydrazonopentan-2,4-dione)-1,3,4-thiadiazole (8)

An ice cold mixture of acetyl acetone (0.01 mol) and sodium acetate (0.01 mol) in 25 ml ethanol was added dropwise with stirring to a solution of the diazonium salt (**7**) over 10 min. The stirring continued for 30 min and the reaction mixture was left 2 h at room temperature. Then the solid product was collected. M.P. 178-180 °C, Yield 67%. IR: 3210(NH), 2900, 2830(CH aliphatic), 2600(SH), 1700(C=O), 1330(C=S). ^{13}C-NMR (DMSO-d_6)δ: 20.3, 21.4(2C, CH_3), 100.2(-<u>C</u>=N), 158.5, 160.6(thiadiazole carbons), 172.0, 174.1(2C, C=O). Anal. Calcd for $C_7H_8N_4O_2S_2$: C,34.43; H,3.28; N,22.95. Found: C,34.07; H,3.12; N,22.36.

Synthesis of 5-mercapto-2-(3,5-dimethyl-1H-pyrazol-4-ylazo)-1,3,4-thiadiazole (9)

A mixture of compound **8** (0.01 mol) and hydrazine hydrate (0.02 mol) was heated under reflux in absolute ethanol for 10-12 h. The solvent was concentrated and the reaction product was allowed to cool. The separated product was filtered off, washed with water, and recrystallized from chloform. M.P. 110-112 °C, Yield 71%. IR: 3200(NH), 2905, 2850(CH aliphatic), 2600(SH), 1630(C=N). ^{13}C-NMR (DMSO-d_6)δ: 17.4, 18.0(2C,CH_3), 56.7, 58.1(2C, -<u>C</u>-CH_3), 99.5(1C, -N-<u>C</u>=C(CH_3))162.6, 164.3(thiadiazole carbons). Anal. Calcd for $C_7H_8N_6S_2$: C,35.00; H,3.33; N,35.00. Found: C,34.31; H,3.10; N,34.58. MS: m/z = 240, 160, 145, 123, 95, 81, 69, 64.

Synthesis of 2-phenylurea-5-mercapto-1,3,4-thiadiazole (10)

A mixture of compound **1** (0.013 mol) and phenylisocyanate (0.013 mol) in abs. ethanol (30 ml) was refluxed for 7 h. The precipitate thus obtained was filtered off and recrystallized from a suitable solvent. M.P. 110-112 °C, Yield 57%. IR: 3220(NH), 3100(CH aromatic), 2650(SH), 1645(C=O), 755,685(aromatic *mono* substituted). ^{13}C-NMR (DMSO-d_6) δ: 128.3, 130.4, 131.7, 132.9(aromatic carbons), 158.1, 160.5(thiadiazole carbons), 170.7(1C, C=O). Anal. Calcd for $C_9H_8N_4OS_2$: C,42.86; H,3.17; N,22.22. Found: C,42.23, H,2.88; N,22.10.

Synthesis of 2-(3-phenyl-1-dihydropyrimidinyl-2,4,6-trione)-5-mercapto-1,3,4-thiadiazole (11)

Malonic acid (0.01 mol) was added to a solution of compound **10** (0.01 mol) in dry benzene (25 ml) and the reaction mixture was refluxed for 8 h. The solid separated on cooling was recrystallized from ether to give the desired product. M.P. 135-137 °C, Yield 65%. IR: 3080(CH aromatic), 2570(SH), 1680(C=O), 770,655(aromatic mono substituted). ^{1}H-NMR ($CDCl_3$)δ: 2.36(s, 2H, CH_2 pyrimidine), 6.21-7.77(m, 5H, Ar-H), 13.16(s, 1H, S-H) (D_2O exchange, disappear). ^{13}C-NMR ($CDCl_3$)δ: 125.1, 127.8, 128.4, 130.0(aromatic carbons), 153.1, 154.1(thiadiazole carbons), 170.2, 173.6, 175.0(3C, carbonyl). Anal. Calcd for $C_{12}H_6N_4O_3S_2$: C,45.71; H,1.90; N,17.78. Found: C,45.77; H,1.7 8; N,17.35.

Synthesis of 2-[3,4-(methylenedioxy)benzylidine]amino-5-mercapto-1,3,4-thiadiazole (12)

A mixture of compound **1** (0.013 mol), abs. ethanol (15 ml), and piperonal (0.013 mol) were refluxed for 7-9 h. After cooling to room temperature, the precipitate was filtered, dried, and then recrystallized from ethanol. M.P. 210-212 °C, Yield 80%. IR: 3100(aromatic C-H), 2920, 2870(CH aliphatic), 2550(SH), 1630(C=N). ^{1}H-NMR (DMSO-d_6) δ: 6.16(s, 2H, CH_2), 7.07(s, 1H, J=7.65, Ar-H, C_2-H), 7.23(d, 1H, J=7.65, Ar-H, C_5-H), 7.56(d, 1H, J=7.65, Ar-H, C_6-H), 8.56(s, 1H, =C-H), 14.43(s, 1H, S-H) (D_2O exchange, disappear). ^{13}C-NMR (DMSO-d_6)δ: 102.3(1C, CH_2), 115.1(1C, =CH-), 128.8-152.4(aromatic carbons), 164.6, 163.8(thiadiazole carbons).

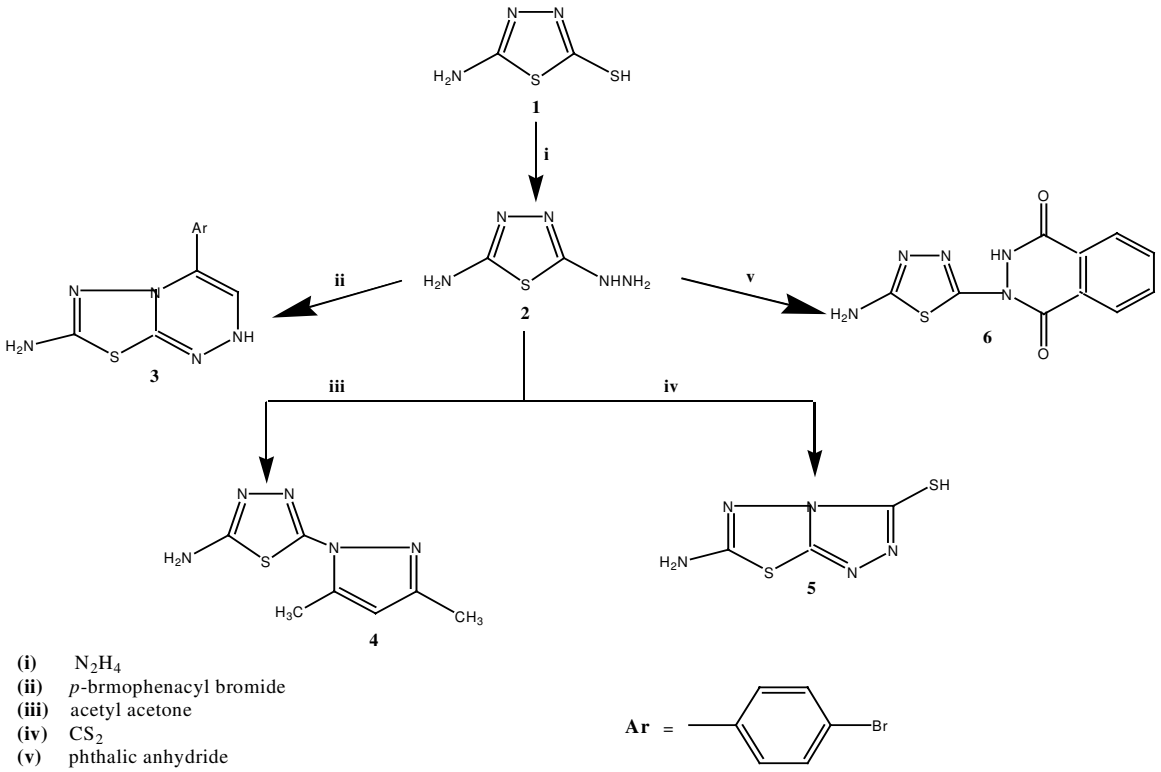
Synthesis of 2(1-pyrrolidinyl -5-mercapto-1,3,4-thiadiazole (13)

A mixture of compound **1**(0.015 mol) and tetrahydrofuran (0.015 mol) in glacial acetic acid (15 ml) were refluxed for 8 h, the solvent was reduced to one third of its volume under reduced pressure and then cooled. The solid separated on cooling was recrystallized from benzene to give the desired product. M.P. 96-98 °C, Yield 52%. IR: 2900, 2870(C-H), 2550(S-H), 1610(C=N). ^{1}H-NMR (DMSO-d_6)δ: 1.89-2.89(m, 4H,

$2CH_2$), 13.24(s, 1H, SH) (D_2O exchange, disappear). ^{13}C-NMR (DMSO-d_6)δ: 46.3, 55.7(2C, $2CH_2$), 153.1, 157.4(thiadiazole carbons). MS: m/z = 187,117, 70 55.

Results and Discussion

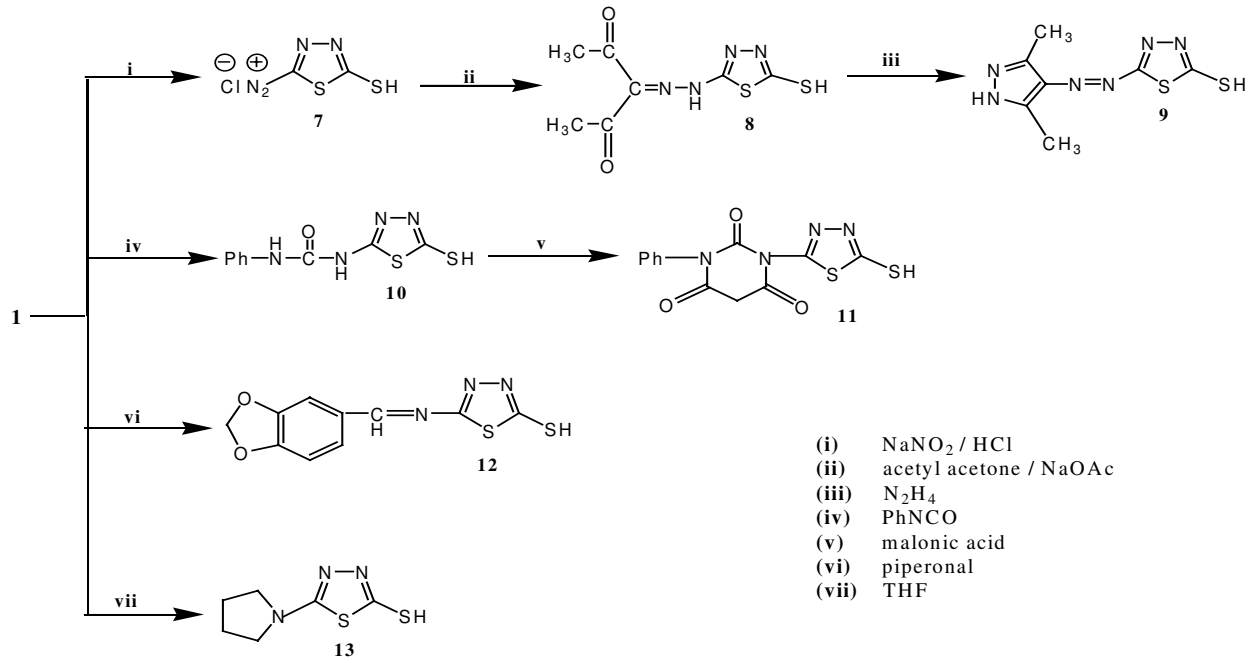
The synthesis start from 2-amino-5-mercapto-1,3,4-thiadiazole (**1**), the thiol group of compound **1** was readily converted into hydrazino derivative (**2**) by heating under reflux with an ethanolic solution of hydrazine hydrate. The resulting 2-amino-5-hydrazino-1,3,4-thiadiazole is used for the synthesis of an interesting derivatives, it is a versatile key intermediate for the synthesis of some fused heterocyclic ring. Thus, the interaction of **2** with *p*-bromophenacyl bromide, acetyl acetone, carbon disulfide, and phthalic anhydride give rise to the formation of the -amino-4-(*p*-bromophenyl)-6H-1,2,4-triazino[5,4-b][1,3,4] thiadiazole (**3**), 2-amino-5-(3,5-dimethyl-1H-pyrazole-1-yl)-1,3,4-thiadiazole (**4**), 2-amino-4-mercapto[1,2,4]triazolo[3,4-b][1,3,4] thiadiazole (**5**) and 2-amino-5-(1,2-dihydrophthalizin-3,6-dione-1-yl)-1,3,4-thiadiazole (**6**), respectively (Scheme 1).



Scheme 1. Synthetic pathways for preparation of compounds **2-6.**

Treatment of thiadiazole (**1**) with sodium nitrite in hydrochloric acid at 0-5 °C afforded the diazonium salt (**7**).The interaction of diazonium salt with active methylene compounds, acetyl acetone, produced 5-mercapto-2-(3-hydrazonopentan-2,4-dione)-1,3,4-thiadiazole (**8**). The 5-mercapto-2-(3,5-dimethyl-1H-pyrazol-4-ylazo)-1,3,4-thiadiazole (**9**) was produced when compound **8** was subjected to heat with hydrazine hydrate (Scheme 2).

Allowing **1**to reflux with phenylisocyanate permits the formation of phenylurea derivative (**10**). When **10** was reacted with malonic acid in refluxing ethanol, the 2-(3-phenyl-1-dihydropyrimidinyl-2,4,6-trione)-5-mercapto-1,3,4-thiadiazole (**11**) was formed (Scheme 2).



Scheme 2. Synthetic pathways for preparation of compounds **7-13.**

On the other hand, condensation of thiadiazole **1** with piperonal in refluxing ethanol forwards towards the formation of the 2-[3,4-(methylenedioxy)benzylidine]amino-5-mercapto-1,3,4-thiadiazole **(12)** (Scheme 2). Finally, boiling thiadiazole **1** with tetrahydrofurane gave the **2**(1-pyrrolidinyl -5-mercapto-1,3,4-thiadiazole **(13)** (Scheme 2).

FT-IR, ^{1}H-NMR, ^{13}C-NMR, and MS spectral data were used to characterize the structure of compounds **3-6**. The IR spectrum of these compounds displayed no absorption derived from –$NHNH_2$ stretching. In the ^{1}H-NMR spectra, new signals at 7.73-7.95 ppm due to aromatic protons of compound **3**, 3.32 and 3.48 ppm, correspond to the 2 –CH_3 groups of compound **4** and 9.67 ppm (exchangeable with D_2O) belonging to –NH- group of compound **6** were recorded. ^{13}C-NMR spectra displayed characteristic signals at 94.3 and 94.8 ppm due to the carbon atoms of triazine ring of compound **3**, 17.6ppm for –CH_3 group of compound **4**, 124.3-130.9 ppm corresponds to aromatic carbons of compound **6**. Mass spectra of compound **3** and **5** were consistent with the proposed structures.

Also FT-IR, ^{1}H-NMR, ^{13}C-NMR, elemental analysis and MS analysis were used to confirm the structure of compounds **8-13**. No absorption band corresponding to –NH_2 group was observed in the IR spectra of the above compounds. Moreover, in the ^{1}H-NMR spectra signals at 6.12-7.77 ppm due to the aromatic protons of compound **11**, 8.56 ppm belonging to the =CH- group of compound **12** and 1.89-2.89 ppm for –CH_2- group of compound **13** were observed. These signals represent more characteristic evidence for the formation of these compounds.

On the other hand, ^{13}C-NMR spectra showed characteristic signals at 172.0 and 174.1(2C, C=O) for compound **8**, 17.4 and 18.0(2C, CH_3) for compound **9**, 170.7(1C, C=O) for compound **10**, 125.1-130.0 ppm due to the aromatic carbons of compound **11**, 102.3 ppm corresponds to –CH_2- group of compound **12**, 46.3ppm and 55.7ppm belonging to –CH_2- of pyrrolidine ring for compound **13**. Mass data for compound **9** and compound **13** give further evidence for the formation of these 2 compounds.

Acknowledgment

The author wishes to thank Dr. Gernot A. Eller, Department of Drug and Natural Product Synthesis, University of Vienna, Vienna, Australia, for performing ^{1}H-NMR, ^{13}C-NMR, elemental and mass analysis of this study.

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