ORIGINAL ARTICLE

A C G publications

Org. Commun. 2:3 (2009) 66-71

organic communications

β-Oxo anilides in heterocyclic synthesis: Synthesis of tri- and tetracyclic heteroaromatic containing a bridgehead nitrogen atom

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(Received November 23, 2008; Revised June 3, 2009; Accepted July 23, 2009)

Abstract: New heterocyclic compounds were synthesized using N-(benzo[d]thiazol-2-yl)-3-oxobutanamide (**1**) as starting material. The condensation of **1** with DMF-DMA by refluxing in xylene gave 3-Acetyl-2H-pyrimido[2,1-b][1,3]benzothiazol-2-one (**3**). Compound **3** was reacted with 2-cyanoethanethioamide, malononitrile, malononitrile/S, phenylhydrazine, and hydrazine to give new azoloazine derivatives.

Keywords:Pyrimido[2,1-b][1,3]benzothiazol-2-one;benzo[d]pyrido[2',3':4,5]pyrimido[2,1-][1,3]thiazole-3-carbonitrile; pyrazolo[3',4':4,5]pyrimido[2,1-b][1,3] thiazole

1. Introduction

Polyfunctionally substituted azoloazines are biologically interesting molecules and their chemistry has considerable attention.[1-3] In the past few years, we have been involved in a program aimed at developing new efficient synthetic approaches for these azoloazines utilizing inexpensive starting materials.[4-7]

2. Results and Discussion

During this phase of our research, we have shown that acetoacetanilide derivative **1** is expected to react with dimethylformamide-dimethylacetal (DMF-DMA) by refluxing in dry xylene to yield the enaminone **2**. However, spectral data and chemical evidence did not match this structure. Since the structure **2** was readily converted to the final product, it was argued as an intermediate. The mass spectrum of **3** showed the molecular ion peak at *m/z* = 244 (M^+)

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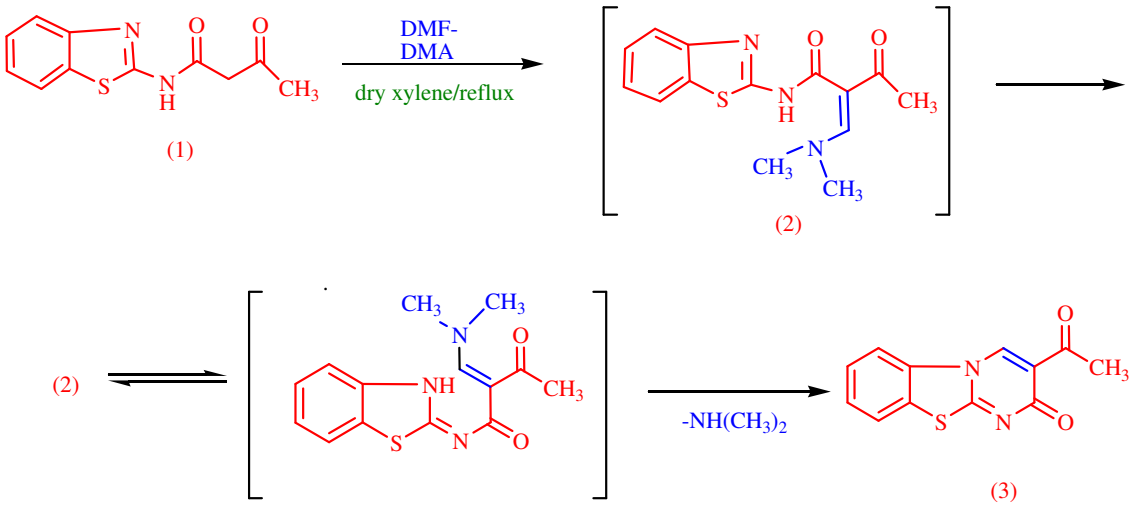
The article was published by Academy of Chemistry of Globe Publications
www.acgpubs.org/OC/index.htm © Published 05/25/2009 EISSN:1307-6175

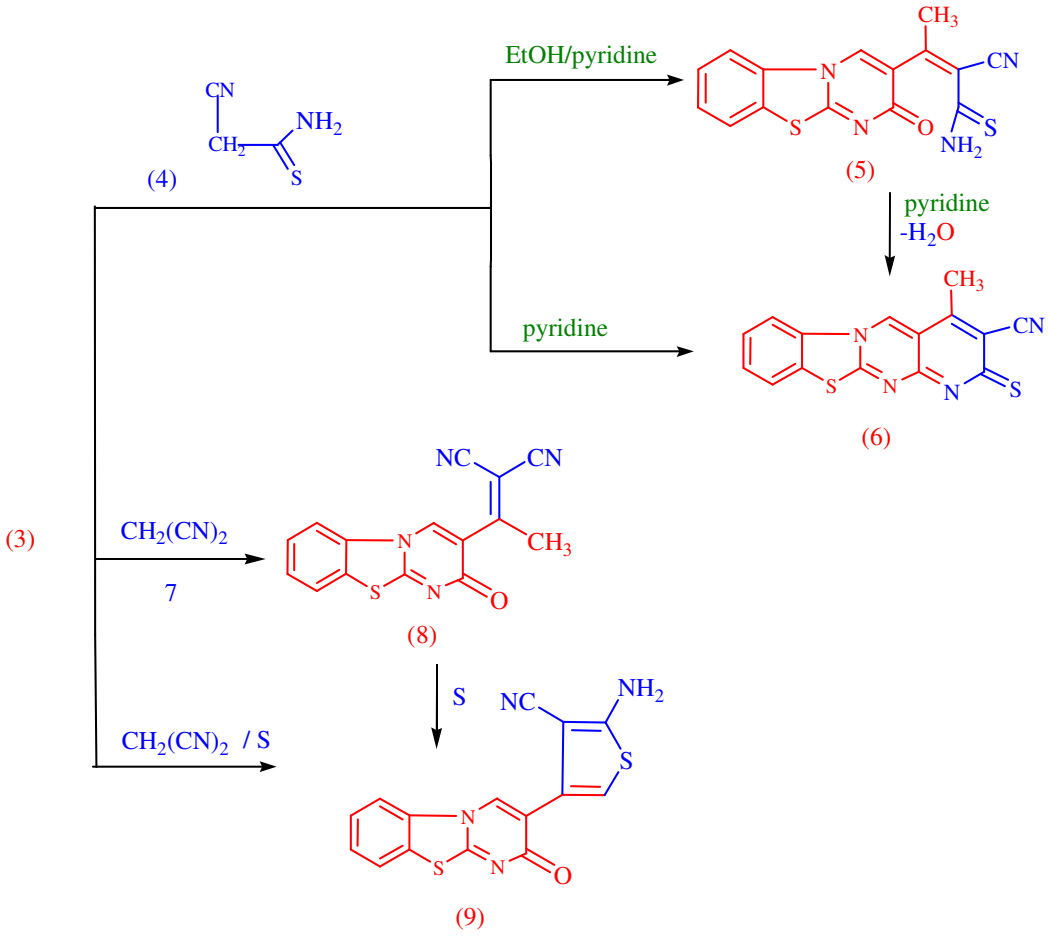
corresponding to benzothiazolone **3**. Also, ^{1}H-NMR spectrum revealed the presence of acetyl group at δ = 2.77 ppm and pyrimidine-H at 8.85 ppm. We thus assume that compound **3** may be formed through intermediate 2, the condensation product of 1 with DMF, followed by removal of a dimethyl amine (Scheme 1).



Scheme 1. Reaction of 1 with DMF-DMA

Structure **3** could be considered as acetyl coumarin for further conversions. For this purpose, condensation of cyanothioacetamide **4** with compound **3** in ethanolic piperidine yield the acyclic structure **5**. The structure of **5** was established on the basis of analytical and spectral data. The infrared spectrum of **5** exhibited absorbance bands at ν 3361, 3185 cm^{-1} for NH_2 and at ν 1677 cm^{-1} for (C=O). Also, the mass spectrum of compound **5** exhibited a molecular ion peak at *m/z* 326 (M^+) corresponding to $C_{15}H_{10}N_4OS_2$. When this reaction was proceed in pyridine, a pyridopyrimidinethione derivative **6** was formed. Compound **6** was confirmed by spectral data. So the IR spectrum showed the disappearance of carbonyl group at ν 1677 and NH_2 at ν 3361, 3185 cm^{-1}. The structure **6** was further confirmed on the basis of boiling the acyclic structure **5** in pyridine solution to form **6**.

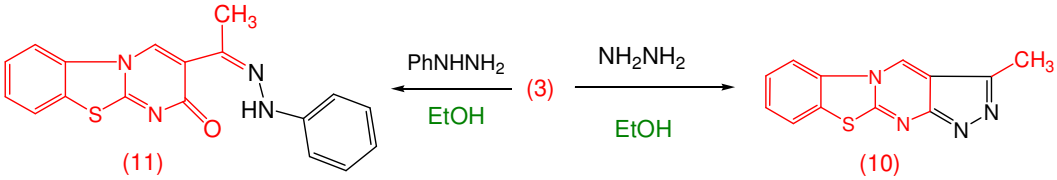
Similarly, condensation of **3** with malononitrile **7** by refluxing ethanolic piperidine afforded the ylidinemalononitrile derivative **8**. Structure **8** was confirmed by spectral data (IR, ^{1}H NMR) and elemental analysis. Compound **8** was reacted with elemental sulfur in ethanolic triethylamine to afford the thiophene derivative **9** which is an application of the Gewald 2-aminothophene synthesis.[8] By a similar approach, compound **9** was obtained by a one-pot reaction of **3** with malononitrile and elemental sulfur in ethanol/triethylamine. Assignment of structure **9** as the reaction product was based on its compatible spectroscopic data. Thus its IR spectrum showed absorption band at ν 3300, 3258 cm^{-1} for NH_2 and ν 2200 cm^{-1} for C≡N group (Scheme 2).



Scheme 2. Reactions of 3 with active methylene reagents

Treatment of compound **3** with hydrazine hydrate afforded the expected tetracyclic compound **10** which was established by the disappearance of the two carbonyl group in the IR spectrum. Its ^{1}H-NMR spectrum showed a singlet at δ = 2.08 ppm belonging to the methyl group and a singlet at δ = 8.19 ppm belonging to the pyrimidine-H. By a similar way, when compound **3** was treated with phenyl hydrazine in ethanol solution afforded compound **11**. The structure of compound **11** was proved by analytical and spectral data.

The infrared spectrum exhibited the presence of amino functional group at ν 3170 cm^{-1} for NH and ν 1662 cm^{-1} for carbonyl group. Its ^{1}H-NMR spectrum showed a broad singlet at δ = 10.46 ppm for NH proton. The mass spectrum revealed a molecular ion peak at *m/z* = 334 (M^{+}) corresponding to the molecular formula $C_{18}H_{14}N_4OS$ (Scheme 3).



Scheme 3. Reactions of 3 hydrazine and phenyl hydrazine

3. Conclusion

In conclusion, pyrimido[2,1-b][1,3]benzothiazol-2-one resulting from the reaction of N-(benzo[d]thiazol-2-yl)-3-oxobutanamide (**1**) with DMF-DMA, was used as an efficient precursor for the synthesis of new heterocycles including benzo[d]pyrido[2',3':4,5]-pyrimido[2,1-b][1,3]thiazole-3-carbonitrile and pyrazolo[3',4':4,5]pyrimido[2,1-b][1,3] thiazole moiety.

4. Experimental

All melting points are uncorrected. IR spectra (KBr) were recorded on a FT-IR 5300 spectrometer (ν, cm^{-1}). The ^1H NMR spectra were recorded in DMSO-d_6 and $CDCl_3$ at 200, 400 MHz on a Varian Gemini NMR spectrometer (δ, ppm) using TMS as an internal standard. EI-MS spectra were obtained on GC Ms-QP 1000 EX mass spectrometer at 70 ev. Elemental analysis was carried out by the Microanalytical Research Center, Faculty of Science, Cairo University and Microanalytical Research Center, Assiut University.

N-(benzo[d]thiazol-2-yl)-3-oxobutanamide (1).

Compound **1** was prepared starting from the reaction of 2-aminobenzothiazole with ethyl acetoacetate according to procedure given in the literature. [9]

3-Acetyl-2H-pyrimido[2,1-b][1,3]benzothiazol-2-one (3):

To a solution of compound **1** (0.01 mol) in dry xylene, dimethylformamide-dimethylacetal (0.01 mol) was added. The reaction mixture was heated under reflux for 6 h, then cooled. The precipitate was filtered off, washed with ether and recrystallized from ethanol to give (**3**; 74%) as pale yellow crystals, m.p. 236-8°C; IR (KBr) ν (cm^{-1}) 3055 (CH-arom), 2925 (CH-aliph), 1672, 1647 (2C=O); ^1H-NMR (400 MHz, $CDCl_3$) δ = 2.77 (s, 3H, $COCH_3$), 7.24-8.16 (m, 4H, Ar-H), 8.85 (s, 1H, pyrimidine-H); MS: m/z(%) = 244 (34.6), 216(46.1), 176(53.8), 148(26.9), 108(23), 90(15.3), 69(15.3), 53(100); Anal Calcd. for $C_{12}H_8N_2O_2S$ (*m/z* 244.27); C, 59.01; H, 3.30; N, 11.47%. Found: C, 59.06; H, 3.34; N, 11.49%.

Preparation of Compounds 5 and 8:

Equimolar amounts of **3** (0.01 mol) and cyanothioacetamide or malononitrile (0.01 mol) in ethanol (30 ml) were treated with a few drops of piperidine and refluxed for 3 h. The solid product formed was filtered off and recrystallized from the proper solvent.

2-Cyano-3-(2-oxo-2H-pyrimido[2,1-b][1,3]benzothiazol-3-yl)but-2-enethioamide (5): It was obtained as brown crystals from acetic acid; yield 75%; m.p. 308-10°C; IR (KBr) ν (cm^{-1})

3361, 3185 (NH_2), 3050 (CH-arom), 2986 (CH-aliph), 2228 (C≡N), 1677 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 1.90 (s, 3H, CH_3), 7.31-8.04 (m, 4H, Ar-H), 8.47 (s, 1H, pyrimidine-H), 14.32 (s, 2H, NH_2); MS: (m/z, %) 327 (16.6), 311(53.3), 298(13), 193(23.3), 177(100), 150(76.6), 122(33.3), 105(13), 78(10).; Anal Calcd. for $C_{15}H_{10}N_4OS_2$ (*m/z*:326.40); C, 55.20; H, 3.09; N, 17.17%. Found: C, 55.21; H, 3.08; N, 17.19%

4-Methyl-2-thioxo-2H-benzo[d]pyrido[2',3':4,5] pyrimido [2,1-b][1,3]thiazole-3-carbonitrile (6):

Method (A): A solution of **3** (1 g) in pyridine (10 mL) was refluxed for 14 h and then allowed to cool. The reaction was poured into cold water and acidified with HCl. The solid product was collected and recrystallized from dioxane/EtOH to give (**6**) in 70% yield.

Method (B): A mixture of compound **3** (0.01 mol), cyanothioacetamide (0.01 mol) in pyridine (10 ml) was refluxed for 14 h, then allowed to cool. The mixture was poured into cold water and acidified with HCl. The solid product was collected and recrystallized from dioxane/EtOH to give (**6**; 70%) as brown crystals, m.p. >360°C; IR (KBr) ν (cm^{-1}) 3020 (CH-arom), 2979 (CH-aliph), 2234 (C≡N); ^{1}H-NMR (200 MHz, DMSO-d_6) δ = 2.63 (s, 3H, CH_3), 7.27-7.98 (m, 4H, Ar-H), 8.55 (s, 1H, pyrimidine-H); Anal Calcd. for $C_{15}H_8N_4S_2$ (*m/z* 308.39); C, 58.42; H, 2.61; N, 18.17%. Found: C, 58.43; H, 2.63; N, 18.19%.

2-[1-(2-oxo-2H-pyrimido[2,1-b][1,3]benzothiazol-3-yl)-ethylidene]-malononitrile (8): Equimolar amounts of **3** (0.01 mol) and malononitrile (0.01 mol) in ethanol (30 ml) were treated with a few drops of piperidine and refluxed for 3 h. The solid product formed was filtered off and recrystallized from ethanol as brown crystals. It was obtained as brown crystals from ethanol; yield 82%; m.p. 250°C; IR (KBr) ν (cm^{-1}) 2905 (CH-aliph), 2208 (C≡N), 1670 (C=O); ^{1}H-NMR 400 MHz (DMSO-d_6) δ = 2.49 (s, 3H, CH_3), 7.28-7.98 (m, 4H, Ar-H), 8.57 (s, 1H, pyrimidine-H); Anal Calcd. for $C_{15}H_8N_4OS$ (*m/z* 292.32); C, 61.63; H, 2.76; N, 19.17%. Found: C, 61.65; H, 2.78; N, 19.18%.

2-Amino-4-(2-oxo-2H-pyrimido[2,1-b][1,3]benzothiazol-3-yl)-thiophene-3-carbonitrile (9):
Method (A): A mixture of **8** (0.01 mol) and elemental sulfur (0.01 mol) in ethanol (30 mL) was treated with little amount of TEA (0.5 ml) and refluxed for 4 h. The solid product that formed after cooling was collected and recrystallized from dioxane/EtOH to give **9**.

Method (B): Equimolar amounts of **3** (0.01 mol), malononitrile (0.01 mol) and elemental sulfur (0.01 mol) in ethanol (30 mL) were treated with little amount of triethylamine (0.5 mL) and refluxed for 4 h. The solid that formed after cooling was collected and recrystallized from dioxane/EtOH to give (**9**; 76%) as buff crystals, m.p. >300 °C; IR (KBr) ν (cm^{-1}) 3300, 3256 (NH_2), 3050 (CH-Ar), 2200 (C≡N), 1690 (C=O); Anal Calcd. for $C_{15}H_8N_4OS_2$ (324.39); C, 55.54; H, 2.49; N, 17.27%. Found: C, 55.56; H, 2.51; N, 17.29%.

General Procedure for the Preparation of Compounds (10,11):

To a suspension of **3** (0.01 mol) in ethanol (30 mL), hydrazine hydrate or phenylhydrazine (0.01 mol) was added. The reaction mixture was refluxed for 4 h, then left to stand. The solid product formed was collected by filtration, washed with water several times and recrysallized from the proper solvent.

3-Methylbenzo[d]pyrazolo[3',4':4,5]pyrimido[2,1-b][1,3]thiazole (10): It was obtained as colorless crystals from ethanol; yield 80%; m.p. 230°C; IR (KBr) (ν cm^{-1}) 3049 (CH-arom),

2950 (CH-aliph); ^{1}H NMR 200 MHz (DMSO-d_6) δ = 2.08 (s, 3H, CH_3), 6.76-8.17 (m, 4H, Ar-H), 8.19 (s, 1H, pyrimidine-H); Anal Calcd. for $C_{12}H_8N_4S$ (*m/z* 240.29); C, 59.98; H, 3.36; N, 23.32%. Found: C, 59.96; H, 3.38; N, 23.36%.

3-(N-(Phenyl-hydrazono)-ethyl)-2H-pyrimido[2,1-b][1,3]benzothiazol-2-one (11): It was obtained as brown crystals from benzene; yield 67%; m.p. 244°C; IR (KBr) (ν cm^{-1}) 3170 (NH), 3054 (CH-arom), 2982 (CH-aliph), 1662 (C=O); ^{1}H NMR 200 MHz ($CDCl_3$) δ = 2.67 (s, 3H, CH_3), 7.11-8.04 (m, 9H, Ar-H), 8.17 (s, 1H, pyrimidine-H), 10.46 (bs, 1H, NH); MS: (m/z; %) 334 (13.7), 185(100), 77(10.3); Anal Calcd. for $C_{18}H_{14}N_4OS$ (*m/z* 334.40); C, 64.65; H, 4.22; N, 16.75%. Found: C, 64.67; H, 4.24; N, 16.78%.

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