Iranian Journal of Organic Chemistry Vol. 8, No. 1 (2016) 1745-1748

Synthesis of substituted benzothaizole from 2,3,4 (tri substituted benzaldehyde) –*N*-(6,7-substituated-1,3-benzothiazol-2 yl) semicarbazone

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Received: January 2016; Revised: January 2016; Accepted: January 2016

Abstract: The reaction of 2,3,4 (trisubstituted benzaldehyde) – *N* - (6,7-substituated-1,3-benzothiazol-2-yl) semicarbazone with Chloroacetyl chloride ,triethlyl amine and DMF leads to 1-(3-chloro-2-(substituted phenyl)-4-oxoazetidin-1-yl)-3-(7-chlorobenzo[d]thiazol-2-yl) urea yield 80%.

Keywords: 2-Amino-7-chloro-(1,3)-benzothaizole, Chloroacetyl chloride ,Triethlyl amine, DMF.

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 special interest because they constitute an important class of natural and nonnatural products, many of which exhibited useful biological activities. Investigation of the 2- amino substituted benzothaizole heterocycles has shown that they possess varied biological properties such as anti tubercular [1], antimicrobial [2], anti-inflammatory [3], anthelmintic [4],Cardiovascular [5], anticancer [6] activity.

In addition, 2-azetidinones derivatives have exhibited wide range of biological activities [7]. Furthermore, they can be used as intermediates in the synthesis of …….

As part of our continuing interest in the construction of novel heterocycles, we now report the results of our studies involving the reactions of 2,3,4 (trisubstituted benzaldehyde) – *N* - (6,7-substituated-1,3-benzothiazol-2-yl) semicarbazone **2.026** and Chloroacetyl chloride ,triethlyl amine which constitutes a synthesis of azetidinones derivatives (Scheme **1**).

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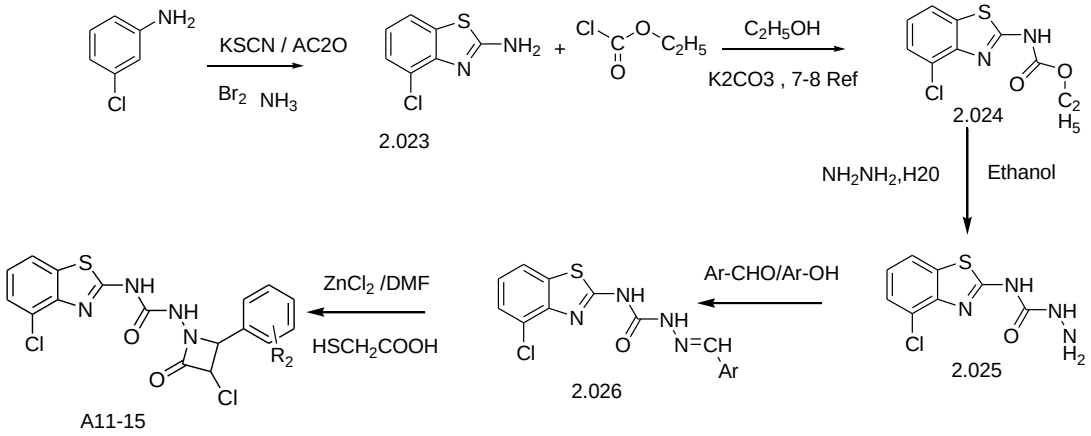
Results and discussion

The structures of compounds A11-15 were deduced from their elemental analyses and their IR, ^{1}H NMR and mass spectra. For example, the ^{1}H NMR spectrum of Ethyl (6,7 -Substituated - 1, 3 - benzothiazol - 2 - yl) carbamate (**2.024**) exhibited multiplet at δ 7.20 for aromatic hydrogen. At δ 8.0, 1.30 and 4.12 singlet peak were observe due to presence of one, three, two proton of NH, CH_3,CH_2 .For *N*- (6,7- Substituted 1,3 - benzothiazo l - 2 -yl) hydrazine carboxamide (**2.025**) exhibited multiplet at δ 7.95 for presence of aromatic proton. Compound number (**2.025**) also showed singlet at δ 6.0 and 2.0 for two and one proton of NH_2, NH, which confirmed the proposed structure. Similarly compound **2.026** exhibited a broad multiplet at δ 7.98 due to presence of aromatic proton. Singlet at δ 3.80 shows the presence of two protons of CH_2 and singlet at δ 8.50 showed the presence of CONH.



Com.	R	R1	R2
A11	H	Cl	4-OCH_3
A12	H	Cl	2-CH_3
A13	H	Cl	3-CH_3
A14	H	Cl	H
A15	H	Cl	2-OCH_3

Scheme 1: Synthetic route for the preparation of compound A 11-15.

The IR spectrum of For ethyl (6,7-Substituated-1,3-benzothiazol-2-yl) carbamate (**2.024**) characteristic absorption band was at 3085 cm^{-1} for (NH), 1608 $cm^{-1}$for (C=N), 1157 $cm^{-1}$for (C-F), 710 $cm^{-1}$for (C-Cl). Similarly compound no **2.025** exhibited characteristic band at 3080 cm^{-1} for (NH), 1602 $cm^{-1}$for (C=N), 1158 $cm^{-1}$for (C-F), 715 $cm^{-1}$for (C-Cl) .

A possible mechanism for the formation of A11-15 shown in (Scheme **2**). Although there is no experimental verification of this.

For substituted aniline the ^{6}th position is the most positive center. As the attack however has been on the 2^{nd} position, which is the electrophilic center, it is probable that thiocyanogen being as pseudo halogen, behaves as an electrophile by attacking this electrophilic center (2^{nd}position). It is equally possible to consider the second position as mounting a nucleophilic attack on thiocyanogen as the substrate.

Conclusion

In summary, we have reported a new procedure for the synthesis of biologically active azetidinones derivatives via reaction of activated 2,3,4 (trisubstituted benzaldehyde) – *N* - (6,7-substituated-1,3-benzothiazol-2-yl) semicarbazone, Chloroacetyl chloride ,triethlyl amine and DMF in excellent yield.

Experimental

General procedure:

Laboratory chemicals were supplied by chemdise chemical Ltd (Rajkot, India). Melting point of synthesized compounds were determined in open capillary and are uncorrected.IR spectra were recorded in Thermo Scientific; NICOLET iS10 spectrophotometer in KBR disc.1HNMR spectra were recorded on 400 MHZ spectrophotometer in DMSO-d6 as a solvent and TMS as an internal stander. The purity of the compounds was checked by TLC. Elemental analyses of all the compounds were in agreement with the calculated values.

The building blocks 2-amino-6,7 substituted benzothiazole [2.023a-c] were prepared according to the reported procedures [8].

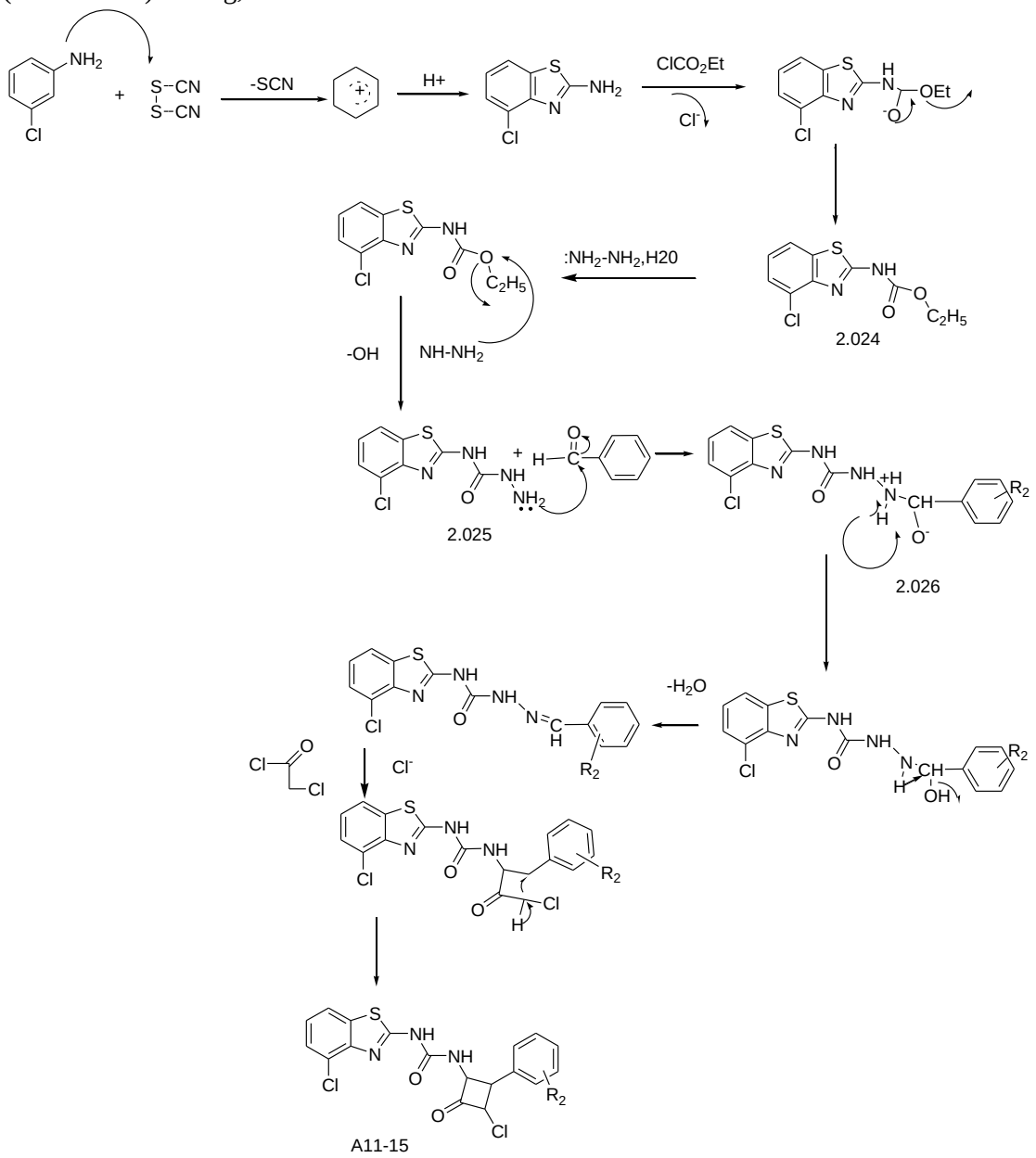
General method for synthesis of Ethyl (6,7-substituted-1,3-benzothiazol-2-yl) carbamate:

2- aminobenzothiazole (0.066 mole) 13.5 g, absolute alcohol 30 ml anhydrous K_2CO_3 (2 g) and ethyl chloroformate (0.0064 mole) 0.7 g, were added under cooled at 0-5^{0}C. The mixture was refluxed for 7- 8 hours at 60-70^{0}C. The solution filtered and the residue was washed with ethanol and the solvent was evaporated under reduced pressure to get the

product as solid which was recrystallized with ethanol.

General method for synthesis of preparation of N-(6,7-Substituted 1,3-benzothiazol-2-yl) hydrazine carboxamide:

Ethyl (6,7-Substituated-1,3-benzothiazol-2-yl) carbamate (0.021 mole) 5.5 g, treated with 4 ml hydrazine hydrate was dissolved in ethanol (30 ml).



Scheme 2: Proposed mechanism for the formation of products.

The reaction mixture was refluxed for 5 hours and cooled to room temperature. The separated carbamoyl hydrazides were filtered and residue was washed with ethanol and recrystallized with alcohol.

General method for synthesis of preparation of 2, 3, 4 (trisubstituted benzaldehyde)-N-(6, 7-substituted-1,3-benzothiazol-2-yl) semicarbazone [2.026]:

5.21 g of N-(6-fluoro-7-chloro-1,3-benzothiazol--yl) hydrazine carboxamide (0.02 mole) was dissolved in absolute ethanol and substituted benzaldehyde (0.02 mole) 2.40 g were added and refluxed for 3 hours and the solvent was removed under reduced pressure to yield Schiff base.

General method for synthesis of Schiff base to azetidinones:

To a solution of Schiff base (0.10 mol) in DMF, chloroacetyl chloride (0.10 mol) and triethlyl amine (0.10 mol) were added and reaction mixture was stirred for 24 hr. The reaction mixture was poured into cooled water and the liberated compound was

extracted with chloroform. Evaporation of the compound afforded the corresponding azetidinones.

1-(3-chloro-2-oxo-4-(p-methoxy) azetidin-1-yl)-3-(7-chlorobenzo[d]thiazol-2-yl)urea (A11):

Pale yellow powder, mp: 170 ^{0}C, Yield 90%. IR (KBr) (νmax/cm^{-1}): 1680 (C=O), 3095(NH), 1615 (C =N), 685 (C-Cl), 725 (C-S-C).^{1}HNMR : δ 7.68 (m, 7 H , Ar- H) , 4.3 (s, 3H , -OCH_3) , 5.98 (s, IH , NH), 4.23 (S , IH , Azetidinone), 3.92 (s, IH, CH-Cl) , 8.42 (s , IH ,CONH). Anal. Calcd. for $C_{18}H_{14}Cl_2N_4O_3S$: C, 49.44; H,3.23; N,12.81. Found:C, 49.43 ; H, 3.21; N, 12.80%.

1-(3-chloro-2-oxo-4-(o-tolyl) azetidin -1-yl)-3-(7-chlorobenzo [d]thiazol-2-yl)urea (A12):

Pale yellow powder, mp: 119 ^{0}C, Yield 85%. IR (KBr) (νmax/cm^{-1}): 1675(C=O), 3095(NH), 1605 (C =N), 680 (C-Cl), 720(C-S-C), ^{1}HNMR : δ 7.68 (m, 7 H , Ar- H) , 2.95 (s, 3H , -OCH_3) , 6.0 (s, IH , NH), 4.23 (S , IH , Azetidinone), 3.95 (s, IH, CH-Cl) , 8.45 (s , IH ,CONH)). Anal. Calcd. for $C_{18}H_{14}Cl_2N_4O_2S$: C, 51.32; H, 3.35; N, 13.30. Found: C, 51.23; H, 3.36 ; N, .13.33 %.

1-(3-chloro-2-oxo-4-(m-tolyl) azetidin -1-yl)-3-(7-chlorobenzo [d]thiazol-2-yl)urea (A13):

Pale yellow powder, mp: 119 ^{0}C, Yield 85%. IR (KBr) 1600 (C=O), 3092 (NH), 1610 (C =N), 1150 (C-F) ;^{1}H NMR 7.84 (m, 6 H , Ar- H) , 2.18 (S, IH , CH_3) , 11.34 (S, IH , NH), 3.56 (S , IH , Azetidinone), 5.67 (S, IH, CH-Cl) ,8.72 (S,IH, CONH) , Anal. Calcd. for $C_{18}H_{14}ClFN_4O_2S$: C, 53.40; H, 3.49; N, 13.84. Found: C, 53.39; H, 3.38; N, 13.83 %.

1-(3-chloro-2-oxo-4-phenylazetidin -1-yl)-3-(7-chlorobenzo [d]thiazol-2-yl)urea (*A14):*

Pale yellow powder, mp: 148 ^{0}C, Yield 68%. IR (KBr) 1652(C=O), 3095(NH), 1602 (C =N), 711(C-Cl), 718(C-S-C); ^{1}HNMR 7.68 (m, 8 H , Ar- H) , 6.10 (s, IH , NH), 4.52 (s , IH , Azetidinone), 4.09 (s, IH, CH-Cl) , 8.53 (s , IH ,CONH). Anal. Calcd. for $C_{17}H_{12}Cl_2N_4O_2S$: C, 50.13; H, 2.97; N, 13.76. Found: C, 50.18; H, 2.95.; N, 13.71 %.

1-(3-chloro-2-oxo-4-(o-methoxy) azetidin-1-yl)-3-(7-chlorobenzo[d]thiazol-2-yl)urea (A15):

Pale yellow powder, mp: 135 ^{0}C, Yield 77%. IR (KBr) 1650(C=O), 3090(NH), 1608(C =N), 717(C-Cl), 730(C-S-C); ^{1}HNMR 7.68 (m, 7 H , Ar- H) , 5.89 (s, IH , NH), 4.51 (s , IH , Azetidinone), 5.40 (s, IH, CH-Cl) , 8.50(s , IH ,CONH). Anal. Calcd. for $C_{18}H_{14}Cl_2N_4O_3S$: C, 49.44; H, 3.23; N, 12.81. Found: C, 51.36; H, 3.34; N, 13.30%.

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