

## Cyanoacetyl Urea in Heterocyclic Synthesis part V: Facile Synthesis of poly-Functionalized Pyrimidines *via* Different Behaviors of its Free Urea Amino Group

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THE poly-functional precursor, cyano-acetyl urea, could be utilized in the synthesis of various pyrimidines utilizing its benzothiazole derivative 1. The free amino group in 1 undergoes different chemical behavior according to the reaction conditions to afford pyrimidines 3,4,5,6,7a,b and 9a,b, respectively.

**Keywords:** 1,3-Benzothiazole, Pyrimidine, Cyanoacetyl urea, small molecules.

### Introduction

Pyrimidines, an important class of heterocycles, occupy a central position due to their presence in genetic material of cells. They occurred widely in nature as substituted or ring fused compounds including nucleotides, thiamine and alloxan. Pyrimidine moiety is also found in various biologically active synthetic compounds, such as, HIV drug zidovudine[1]. As pyrimidine is a basic nucleus in DNA & RNA, it has been found to be associated with diverse biological activities and its derivatives have attracted much attention due to their remarkable and prominent pharmacological activity[2].

Among various pyrimidine derivatives, the synthesis of pyrimidine-2,4-diones remains an area of current interest due to the presence of such moiety in a large number of biologically important compounds [3-5]. Recently, we synthesized a superabsorbent which could be used to absorb urea from urine [6] as we are interested in utilizing biomass building block in organic synthesis. We previously prepared cyanoacetyl urea and its benzothiazole derivative 1 and used them as versatile precursors for synthesis of many biologically active small molecules [7]. Utility of 1 in the synthesis of thymine analogs and condensed aza-heterocycles has been also reported [8]. In continuation, we explored these approaches to prepare other difficulty accessible pyrimidones.

### Results and Discussion

It has been found that when 2-(benzo[d]thiazol-2-yl)-N-carbamoyl acetamide (1) condensed with 4-chloro-benzaldehyde in ethanolic piperidine, it afforded the corresponding arylidene 2 in an excellent yield (Scheme 1). Its <sup>1</sup>H-NMR spectrum showed the ylidene singlet at  $\delta$  7.9 ppm. Its IR spectrum and elemental analysis are in accordance with this structure. In addition, its mass spectral data showed a molecular ion peak ( $M^+$ ) compatible with its formula  $C_{17}H_{12}ClN_3O_2S$  at  $m/z = 357$  (30%).

Compound 2 underwent 1,6-cyclization by refluxing in DMF, in the presence of triethylamine, to afford a product which showed a molecular ion peak similar to that of the parent compound 2. The absence of singlet signal of ylidene proton and the presence of two new doublet signals at  $\delta$  4.9 ppm and  $\delta$  5.3 ppm, each signal integrates to 1H, were shown in its <sup>1</sup>H-NMR spectrum. Accordingly, dihydro pyrimidine structure of compound 3 was given to this obtained product (Scheme 1).

Benzothiazolyl uracil derivative 4, was obtained upon heating compound 1 in triethyl orthoformate. It seems that free urea amino group in the ethoxy ylidene intermediate of 4 prefers replacement of the ethoxy group as eliminated ethanol instead of its addition behavior to afford dihydropyrimidine (3).

Upon refluxing compound 1 in acetic anhydride containing zinc chloride as a catalyst,

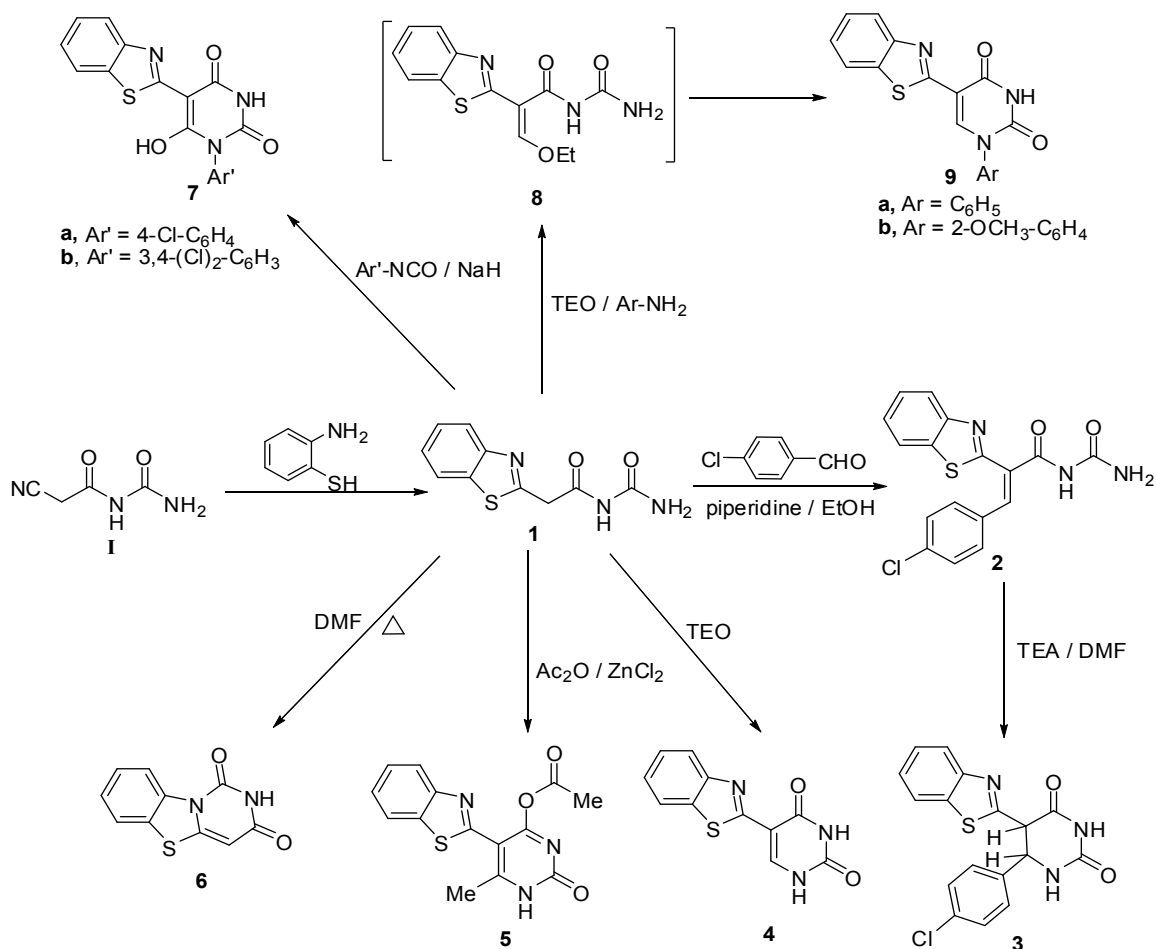
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a new compound was obtained. The mass spectrum of this compound showed a molecular ion peak ( $M^+$ ) as base peak at  $m/z = 301$  (100%). Its  $^1\text{H-NMR}$  spectrum lacked the characteristic signals of methylene and ureido  $\text{NH}_2$  [8] and revealed only one  $\text{D}_2\text{O}$  exchangeable, singlet signal, it also showed benzothiazole signals and two methyl singlet signals at  $\delta$  2.4 ppm and  $\delta$  2.6

ppm, respectively. Based on this information, in addition to its IR spectrum and the microanalytical data, the 4-O-acetylateduracil structure of compound 5 was given to this product [9] (Scheme1). Product 5 was formed via acetylating the active methylene group in compound 1 with subsequent condensation with free amino group.



Scheme 1.

On the other hand, when compound **1** was refluxed in DMF, a new compound was obtained. Its  $^1\text{H-NMR}$  showed the absence of methylene protons signal at  $\delta$  4.2 ppm in its parent spectrum and it showed also the presence of a signal at 6.2 ppm (1H) along with one  $\text{D}_2\text{O}$  exchangeable signal (1H) at  $\delta$  11.6 ppm. In addition, its IR spectrum revealed the presence of  $\text{C}=\text{O}$  absorption peaks while its mass spectral data showed molecular ion peak at  $m/z = 218$  (95%). Based on the previous data, the structure 1*H*-benzo[4,5]thiazolo[3,2-*c*]pyrimidine-1,3(2*H*)-dione (**6**) was established to

this product (Scheme 1). Compound **6** is assumed to be formed *via* self cyclization involving the nucleophilic attack of benzothiazole NH on  $\text{C}=\text{O}$  group of the ureido residue with evolution of ammonia, a result in accordance with previous reports [7].

Moreover, when compound **1** was allowed to react with two different aryl isocyanates in dry dimethyl formamide and sodium hydride, new compounds were obtained with evolution of ammonia gas. Their  $^1\text{H-NMR}$  showed aromatic

protons along with D<sub>2</sub>O exchangeable signals. Meantime, their mass spectra gave molecular ion peaks, in each case, equal to the sum of the two reactants minus ammonia. Based on these data, IR spectrum and microanalytical analysis of these products, their structure 5-(benzo[d]thiazol-2-yl)-6-hydroxy-1-arylpyrimidine-2,4(1*H*,3*H*)-dione **7a,b** were established (Scheme1). They are assumed to be formed through addition of the active methylene on the corresponding isocyanate to form a 1:1 adduct which subsequently cyclized *via* elimination of the urea amino group to afford the final product.

Compound **1** was treated with triethyl orthoformate in the presence of aniline in equimolar ratio and a product with molecular formula C<sub>17</sub>H<sub>11</sub>N<sub>3</sub>O<sub>2</sub>S (m/z =321, M<sup>+</sup>100%) was obtained. Its <sup>1</sup>H-NMR revealed the absence of the ureido NH<sub>2</sub> and active methylene signals and the presence of additional signals of aromatic protons to those of benzothiazole moiety, along with the characteristic singlet (1H) at δ 8.6 ppm similar to that previously detected for the pyrimidine 6-H [8]. These data in addition to the microanalytical analysis caused the 5-(benzothiazole-2-yl) uracil derivative **9a** to be assumed for this product (Scheme 1). Similarly, when the reaction was repeated with *O*-anisidine, the corresponding derivative **9b** was obtained in a fairly good yield (Scheme 1). It is assumed that, compound **1** reacted with triethyl orthoformate to give the intermediate **8** which reacted with aniline via loss of ethyl alcohol, and followed by subsequent self cyclization with emission of ammonia to afford the final products **9a,b**, a result in accordance with previously reported findings [10]. It is worth to mention that, reaction of **1** with triethyl orthoformate in absence of aniline proceeded via the same intermediate **8** which underwent self cyclization with loss of ethyl alcohol to give compound **4**.

### Experimental

Melting points are uncorrected and were taken on an electrothermal 9100 apparatus; IR spectra were recorded with a Carl Zeiss spectrophotometer, model UR 10 in KBr pellets. <sup>1</sup>H-NMR spectra were determined with a Jeol instrument (internal TMS). Mass spectra were recorded with Finigan SSQ 7000 mass spectrometer. Microanalysis was performed by the Central Service Laboratory at Cairo University and the Microanalytical Unit at the National Research Centre.

#### (*Z*)-2-(Benzo[d]thiazol-2-yl)-*N*-carbamoyl-3-(4-chlorophenyl)acrylamide (**2**)

Compound **1** (10 mmole, 2.35g) was refluxed with 4-chlorobenzaldehyde (10 mmole, 1.4g) in ethyl alcohol (30 ml) in presence of piperidine (3 drops) as a catalyst for 2h. A precipitate was formed during the reaction course, filtered off and crystallized to give compound **2**, m.p 226-227 °C, yield 85% (ethanol).

IR(KBr), ν/cm<sup>-1</sup> 3365-3150 NH<sub>2</sub>, NH, 1730, 1690 (2C=O).

<sup>1</sup>H-NMR [DMSO-*d*<sub>6</sub>] (D<sub>2</sub>O exchangeable), δ, 7.10-7.80 (m, 9H, C<sub>6</sub>H<sub>4</sub>, benzothiazole 5-H, 6-H,ylidene H and NH<sub>2</sub>), 8.10-8.30 (m,2H benzothiazole 4-H and 7-H, 11.00 (s,1H, NH).

MS *m/z* (M<sup>+</sup> 357,30%). Anal. Calcd for C<sub>17</sub>H<sub>12</sub>ClN<sub>3</sub>O<sub>2</sub>S (357.81): C, 57.06%; H, 3.38%; Cl, 9.91%; N, 11.74%; S, 8.96%.

Found: C, 57.12%; H, 3.25%; Cl, 9.78%; N, 11.62%; S, 8.81%.

#### 5-(Benzo[d]thiazol-2-yl)-6-(4-chlorophenyl) dihydropyrimidine-2,4(1*H*,3*H*)-dione (**3**):

Compound **2** (10 mmole, 3.57g) was refluxed in dimethylformamide (10 ml) in presence of triethylamine (2 drops) as a catalyst for 30 min. The reaction mixture was then partially concentrated, cooled and the solid formed was filtered off, and crystallized to give compound **3**, m.p 267-268 °C, yield 20% (ethanol).

IR(KBr), ν/cm<sup>-1</sup> 3250-3080 2NH, 1710, 1700 (2C=O).

<sup>1</sup>H-NMR [DMSO-*d*<sub>6</sub>] (D<sub>2</sub>O exchangeable), δ, *J*= 11 Hz, 4.90 (d,1H, pyrimidine 5-H), *J*= 11 Hz, 5.25 (d,1H, Pyrimidine 6H), 7.40-7.60 (m, 6H, C<sub>6</sub>H<sub>4</sub>, benzothiazole 5-H,6-H), 8.10 (m, 2H benzothiazole 4-H and 7-H), 8.70 ppm (s,1H,NH), 10.60 (s,1H, NH). MS *m/z* (M<sup>+</sup> 357,50%).

Anal. Calcd. for C<sub>17</sub>H<sub>12</sub>ClN<sub>3</sub>O<sub>2</sub>S (357.81): C, 57.06%; H, 3.38%; Cl, 9.91%; N, 11.74%; S, 8.96%.

Found: C, 57.13%; H, 3.29%; Cl, 9.22%; N, 11.63%; S, 8.77%.

#### 5-(Benzo[d]thiazol-2-yl)pyrimidine-2,4-(1*H*,3*H*) dione (**4**):

Compound **1** (10 mmole, 2.35g) was refluxed in triethylorthoformate (10 ml) for 30 min. After cooling, the formed precipitate was filtered off

and crystallized to give compound **4**, m.p >300 °C, yield 70% (acetic acid).

IR(KBr),  $\nu/\text{cm}^{-1}$  3200-2800 (2NH), 1720, 1680 (2C=O).

$^1\text{H-NMR}$  [DMSO- $d_6$ ] ( $\text{D}_2\text{O}$  exchangeable),  $\delta$ , 7.30-7.50 (m, 2H, benzothiazole 5-H, 6-H), 7.90-8.00 (m, 2H, benzothiazole 4-H and 7-H), 8.50 (s, 1H, Pyrimidine 6-H), 11.75, 11.80 (2s, 2H, 2NH).

MS (70ev):  $m/z$  ( $\text{M}^+$  245, 35%).

Anal. Calcd. for  $\text{C}_{11}\text{H}_7\text{N}_3\text{O}_2\text{S}$  (245.26): C, 53.87%; H, 2.88%; N, 17.13%; S, 13.07%.

Found: C, 53.62%; H, 2.72%; N, 16.09%; S, 12.82%.

*5-(Benzo[d]thiazol-2-yl)-6-methyl-2-oxo-1,2-dihydropyrimidine-4-yl acetate (5):*

Compound **1** (10 mmole, 2.35g) was refluxed in acetic anhydride (20 ml) containing zinc chloride (0.5 g) for about 1 h. The precipitate formed during reflux was filtered off and crystallized to give compound **5**, m.p 257°C, yield 30% (ethyl alcohol).

IR(KBr),  $\nu/\text{cm}^{-1}$  3450-3400 NH, 1685, 1640 (2C=O).

$^1\text{H-NMR}$  [DMSO- $d_6$ ] ( $\text{D}_2\text{O}$  exchangeable),  $\delta$ , 2.40 (s, 3H,  $\text{CH}_3$ ), 2.60 (s, 3H,  $\text{CH}_3$ ), 7.50-7.60 (m, 2H, benzothiazole 4-H and 5-H), 8.10 (m, 1H, benzothiazole 4-H), 9.20 (m, 1H, benzothiazole 7-H), 12.60 (s, 1H, NH).

MS (70ev):  $m/z$  ( $\text{M}^+$  301, 100%).

Anal. Calcd. For  $\text{C}_{14}\text{H}_{11}\text{N}_3\text{O}_3\text{S}$  (301.32): C, 55.80%; H, 3.68%; N, 13.95%; S, 10.64%.

Found: C, 55.69%; H, 3.59%; N, 13.80%; S, 10.50%.

*5-(Benzo[d]thiazolo[3,2-c]pyrimidine-2,4-dione (6):*

Compound **1** (10mmole, 2.35g) was refluxed in DMF(10 ml) for 1h. After partial concentration and cooling, a precipitate was formed, filtered off and crystallized to give compound **6**, m.p 287-289 °C, yield 80 % (acetic acid).

IR(KBr),  $\nu/\text{cm}^{-1}$  3430 NH, 1725, 1642 (2C=O).

$^1\text{H-NMR}$  [DMSO- $d_6$ ] ( $\text{D}_2\text{O}$  exchangeable),  $\delta$ , 6.20 (s, 1H, Pyrimidine 4-H), 7.30-7.40 (m, 2H, benzothiazole 5-H and 6-H), 7.90 (m, 1H,

benzothiazole 4-H), 8.50 (m, 1H benzothiazole 7-H), 11.60 (s, 1H, NH).

MS (70ev):  $m/z$  ( $\text{M}^+$  218, 95%).

Anal. Calcd. for  $\text{C}_{10}\text{H}_6\text{N}_2\text{O}_2\text{S}$  (218.23): C, 55.04%; H, 2.77%; N, 12.84%; S, 14.69%.

Found: C, 54.88%; H, 2.66%; N, 12.68%; S, 14.90%.

*5-(Benzo[d]thiazol-2-yl)-1-aryl-6-hydroxypyrimidine-2,4(1H,3H)-dione(7a,b):*

*General procedure:*

To a solution of compound **1** (10 mmole, 2.35g) in 10 ml dry DMF in the presence of sodium hydride (10 mmol) at 50 °C, a solution of the proper arylisocyanate (10 mmole) in 5ml dry DMF was dropped over within 30 min. with stirring. Stirring was kept for further 1h., then HCl (50% v/v) was added to the reaction mixture till neutralization. Thus, precipitate was formed, filtered off, washed with warm water and finally crystallized.

*5-(Benzo[d]thiazol-2-yl)-1-(4-chlorophenyl)-6-hydroxypyrimidine-2,4(1H,3H)-dione (7a):*

m.p >300 °C, yield 85% (DMF).

IR(KBr),  $\nu/\text{cm}^{-1}$  3470-3100 NH, OH, 1745, 1670 (2C=O).

$^1\text{H-NMR}$  [DMSO- $d_6$ ] ( $\text{D}_2\text{O}$  exchangeable),  $\delta$ , 7.30-7.70 (m, 6H,  $\text{C}_6\text{H}_4$  and benzothiazole 5-H and 6-H), 8.00 (m, 1H benzothiazole 4-H), 8.60 (m, 1H benzothiazole 7-H), 11.50 (s, 1H, NH), 12.50 (s, 1H, OH).

MS (70ev):  $m/z$  ( $\text{M}^+$  371, 40%).

Anal. Calcd. for  $\text{C}_{17}\text{H}_{10}\text{ClN}_3\text{O}_3\text{S}$  (371.80): C, 54.92%; H, 2.71%; Cl, 9.54%; N, 11.30%; S, 8.62%.

Found: C, 54.81%; H, 2.65%; Cl, 9.43%; N, 11.15%; S, 8.52%.

*5-(Benzo[d]thiazol-2-yl)-1-(3,4-dichlorophenyl)-6-hydroxypyrimidine-2,4(1H,3H)-dione (7b):*

m.p >300 °C, yield 85% (DMF).

IR(KBr),  $\nu/\text{cm}^{-1}$  3450-3100 NH, OH, 1740, 1680 (2C=O).

$^1\text{H-NMR}$  [DMSO- $d_6$ ] ( $\text{D}_2\text{O}$  exchangeable),  $\delta$ , 7.40-8.20 (m, 6H,  $\text{C}_6\text{H}_3$  and benzothiazole 5-H, 6-H and 4-H), 8.60 (m, 1H benzothiazole 7-H), 11.50 (s, 1H, NH), 12.50 (s, 1H, OH).

MS (70ev):  $m/z$  ( $M^+$  406, 20%).

Anal. Calcd. for  $C_{17}H_9Cl_2N_3O_3S$  (406.24): C, 50.26%; H, 2.23%; Cl, 17.45%; N, 10.34%; S, 7.89%.

Found: C, 50.12%; H, 2.19%; Cl, 17.31%; N, 10.28%; S, 7.69%.

*1-Aryl-5-(benzothiazol-2-yl)-3H-pyrimidine-2,4-dione (9a,b)*.

Compound 1 (10mmole, 2.35g) was refluxed with the appropriate aniline derivative (10 mmole) and triethylortho formate (10 mmole, 1.48g) in dry dimethylformamide (10 ml) for 2 h. The precipitate formed during the reaction course was filtered off and crystallized.

*5-(Benzo[d]thiazol-2-yl)-1-phenylpyrimidine-2,4-(1H,3H)-dione (9a)*:

m.p >300 °C, yield 75% (DMF).

IR(KBr),  $\nu/cm^{-1}$  3450-3350 NH, 1740, 1685 (2C=O).

$^1H$ -NMR [DMSO- $d_6$ ] ( $D_2O$  exchangeable),  $\delta$ , 7.40-7.65 (m, 7H,  $C_6H_5$  and benzothiazole 5-H, and 6-H), 7.90 (m, 1H benzothiazole 4-H), 8.20(m, 1H benzothiazole 7-H), 8.65(s, 1H, Pyrimidine 6-H), 12.25(s, 1H, NH).

MS (70ev):  $m/z$  ( $M^+$  321, 100%).

Anal. Calcd. for  $C_{17}H_{11}N_3O_2S$  (321.35): C, 63.54%; H, 3.45%; N, 13.08%; S, 9.98%.

Found: C, 63.42%; H, 3.30%; N, 13.18%; S, 9.80%.

*5-(Benzo[d]thiazol-2-yl)-1-(2-methoxyphenyl)pyrimidine-2,4(1H,3H)dione(9b)*:

m.p >300 °C, yield 80% (DMF).

IR(KBr),  $\nu/cm^{-1}$  3450-3360 NH, 1735, 1690 (2C=O).

$^1H$ -NMR [DMSO- $d_6$ ] ( $D_2O$  exchangeable),  $\delta$ , 7.20-7.70 (m, 6H,  $C_6H_4$  and benzothiazole 5-H, and 6-H), 7.90 (m, 1H benzothiazole 4-H), 8.10 (m, 1H benzothiazole 7-H), 8.60 (s, 1H, Pyrimidine 6-H), 12.30 (s, 1H, NH).

MS (70ev):  $m/z$  ( $M^+$  351.07, 100%).

Anal. Calcd. for  $C_{18}H_{13}N_3O_3S$  (351.38): C, 61.53%; H, 3.73%; N, 11.96%; S, 9.13%.

Found: C, 61.39%; H, 3.66%; N, 11.81%; S, 8.99%.

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### سيانو أسيتيل يوريا في تخليق حلقات غير متجانسة (الجزء الخامس): تخليق سهل للبيريميدينات متعددة المجموعات الوظيفية من خلال سلوكيات مختلفة لمجموعة أمين اليوريا الحرة

هدى صبرى عثمان أحمد<sup>١</sup>، ماهر عبد العزيز الحشاش<sup>٢</sup> و جلال عبد المعين محمود نوار<sup>١</sup>  
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تم استخدام المادة الأولية، متعددة المجموعات الوظيفية، سيانو أسيتيل يوريا، في تخليق بيريميدينات متنوعة، عن طريق استغلال مشتقها المحتوى على البينزوسيازول ١. وقد سلكت مجموعة الأمين الحرة في ١ سلوكيات كيميائية مختلفة طبقاً لظروف التفاعل، مما أنتج البيريميدينات ٣، ٤، ٥، ٦، ٧، ٩، ب، أ، على الترتيب.