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Received July 6, 1989

Methyl 2-benzoylamino-3-dimethylaminopropenoate (**2**) was introduced as a new reagent for the preparation of fused pyrimidinones **4** from heterocyclic  $\alpha$ -amino compounds in acetic acid. In this manner, derivatives of pyrido[1,2-*a*]pyrimidine **4a,b,f**, pyrimido[1,2-*b*]pyridazine **4g**, pyrimido[1,2-*c*]pyrimidine **4j**, pyrazino[1,2-*a*]pyrimidine **4k**, thiazolo[2,3-*b*]pyrimidine **4l**, pyrazolo[1,5-*a*]pyrimidine **4m**, and 1,2,4-triazolo[1,5-*a*]pyrimidine **4n** were prepared.

*J. Heterocyclic Chem.*, **27**, 359 (1990).

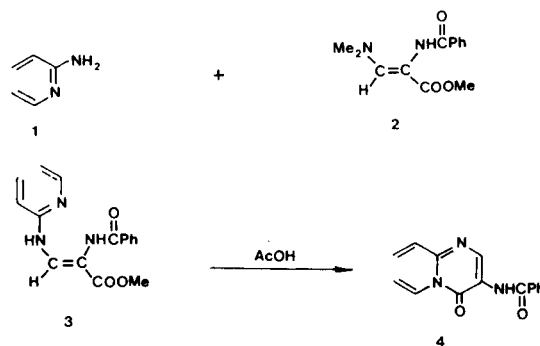
It has been observed earlier, that pyrido[1,2-*b*]pyrimidine and thiazolo[2,3-*b*]pyrimidine derivatives are formed in the reaction of 4-ethoxyalkylidene-2-phenyl-2-oxazolin-5-ones with aminopyridine derivatives and 2-aminothiazole in refluxing ethanol [1]. Similarly, we have observed in our studies of transformations of 4-heteroarylaminomethylene-2-phenyl-5(4*H*)-oxazolones, prepared from *N*-heteroarylformamidines and 5-oxo-2-phenyl-1,3-oxazole in acetic anhydride, into  $\beta$ -heteroaryl-amino- $\alpha,\beta$ -dehydro- $\alpha$ -amino acid derivatives [2-4], that 4-(6-chloro-3-pyridazinylamino)methylene-2-phenyl-5(4*H*)-oxazolone cyclizes in the presence of sodium methoxide in methanol into a pyrido[1,2-*b*]pyridazine derivative [4].

In order to avoid this cyclization, we have introduced recently methyl 2-benzoylamino-3-dimethylaminopropenoate (**2**) [4,5], which has been used previously for the preparation of 2-benzoylamino-3-(2-indolyl)propenoate [5], also for the preparation of  $\beta$ -heteroaryl-amino- $\alpha,\beta$ -dehydro- $\alpha$ -amino acid derivatives under mild conditions starting from primary or secondary heterocyclic amines [4]. It turned out, that this compound is a versatile reagent for the synthesis of various classes of organic compounds, such as 3-arylamino-2-benzoylamino propenoates in the preparation of substituted arylaminoalanines [6], 3-benzoylamino-2*H*-pyran-2-ones [7], benzoylamino substituted 7*H*-pyrano[2,3-*d*]pyrimidines, 1*H*,6*H*-pyrano[2,3-*c*]pyrazoles and 2*H*-1-benzopyran derivatives [8].

In this communication we report, as a further extension of our investigations in this area, the synthesis of fused benzoylamino substituted pyrimidinones **4** from heterocyclic  $\alpha$ -amino compounds **1** and methyl 2-benzoylamino-3-dimethylaminopropenoate (**2**). In this connection we selected the following heterocyclic  $\alpha$ -amines: 2-aminopyridine (**1a**) and its 4-methyl (**1b**), 6-methyl (**1c**), 5-nitro (**1d**), 3,5-dibromo (**1e**) and 3-amino (**1f**) derivatives, 3-amino-6-chloropyridazine (**1g**), 2-amino-4,6-dimethyl (**1h**), 4-amino-2,6-dimethyl (**1i**), and 4-amino-2,6-dihydroxypyrimidine

(**1j**), 2-aminopyrazine (**1k**), 2-aminothiazole (**1l**), 3-amino-4-cyanopyrazole (**1m**), 3-amino-1*H*-1,2,4-triazole (**1n**), 3-amino-oxazole (**1o**), and its 5-methyl derivative (**1p**) (Scheme 1). When these compounds are heated with **2** under more drastic reaction conditions, the cyclization of the intermediates **3** could take place to give the fused pyrimidines with a bridgehead nitrogen atom of the type **4**. In this way pyrido[1,2-*a*]pyrimidine derivatives **4a,b**, pyrimido[1,2-*b*]pyridazine derivative **4g**, pyrimido[1,2-*c*]pyrimidine derivative **4j**, pyrazino[1,2-*a*]pyrimidine derivative **4k**, thiazolo[2,3-*b*]pyrimidine derivative **4l**, pyrazolo[1,5-*a*]pyrimidine derivative **4m**, and triazolo[1,5-*a*]pyrimidine derivative **4n** are formed, respectively. 2,3-Diaminopyridine (**1f**) reacted at both amino group to give **4f** with the aminopropenoic acid side chain attached at position 9 (Scheme 2).

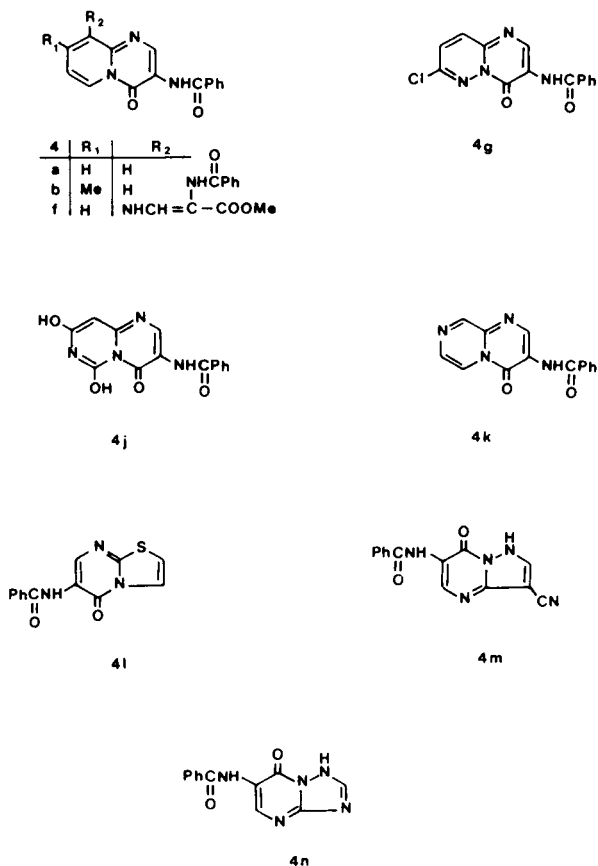
Scheme 1



Het :

- |                                  |                                      |
|----------------------------------|--------------------------------------|
| a) pyridyl - 2                   | i) 2,6 - dimethylpyrimidinyl - 4     |
| b) 4 - methylpyridyl - 2         | j) 2,6 - dihydroxypyrimidinyl - 4    |
| c) 6 - methylpyridyl - 2         | k) pyrazinyl - 2                     |
| d) 5 - nitropyridyl - 2          | l) thiazolyl - 2                     |
| e) 3,5 - dibromopyridyl - 2      | m) 4 - cyanopyrazolyl - 3            |
| f) 3 - aminopyridyl - 2          | n) 1 <i>H</i> -1,2,4 - triazolyl - 3 |
| g) 6 - chloropyridazinyl - 3     | o) isoxazolyl - 3                    |
| h) 4,6 - dimethylpyrimidinyl - 2 | p) 5 - methylisoxazolyl - 3          |

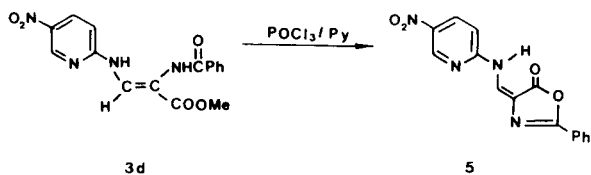
Scheme 2



On the other hand, sterically more hindered amines or compounds with electronegative substituents attached to heterocyclic ring, such as 6-methyl (**1c**), 5-nitro (**1d**), 3,5-dibromo (**1e**) pyridine derivatives, 4,6-dimethyl (**1h**) and 2,6-dimethyl (**1i**) pyrimidine derivatives did not cyclize under these conditions and only the corresponding intermediates **3c,d,e,h,i** were isolated. In the isoxazole series only the intermediates **3o,p** could be isolated, while by prolonged reaction time decomposition was observed most probably due to the instability of the isoxazole ring.

In order to bring about the cyclization of less reactive compounds, which did not cyclize under these conditions, we heated 2-amino-5-nitropyridine (**1d**) in polyphosphoric acid for several hours at 100-120°. However, under these conditions only the cyclization of the side chain was observed to produce the oxazolone derivative **5** (Scheme 3).

Scheme 3



The structure determination of the noncyclized compound **3** and fused pyrimidones **4** is based on the differences in elemental analyses and <sup>1</sup>H nmr spectral characteristics. The most significant feature is CHNH structural element of the side chain in compounds **3**, for which two doublets appear in the <sup>1</sup>H nmr spectra with a large coupling constant  $J_{CHNH} = \sim 10$  Hz, while the corresponding protons in the fused systems **4** appear as singlets.

## EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The <sup>1</sup>H nmr spectra were obtained on a JEOL FX 90 Ω spectrometer, and microanalyses for C, H, and N on a Perkin-Elmer Analyser 240 C.

The Reaction Between Heterocyclic Amines and Methyl 2-Benzoylamino-3-dimethylaminopropenoate. The Synthesis of Fused Pyrimidones or Methyl 3-Heteroaryl-amino-2-benzoylamino-propenoates.

## General Procedure.

To a solution of heterocyclic amine **1** (0.005 mole) in acetic acid (6 ml) **2** (0.005 mole) was added and the mixture was heated under reflux for several hours. The reaction was followed by tlc (DC-Alufolien Kieselgel 60 F 254, 0.2 mm, E. Merck, and chloroform/methanol, 10:1, as solvent). After the reaction was completed, acetic acid was evaporated *in vacuo*, the solid residue washed with cold water (2 ml) and recrystallized from an appropriate solvent to give **3** or **4**.

The following compounds were prepared in this manner:

3-Benzoylamino-4-oxo-4H-pyrido[1,2-a]pyrimidine (**4a**).

This compound was prepared from **1a**, 5 hours of reflux, in 87% yield, mp 194-195° (from ethanol), lit [1] mp 196.5-198°.

3-Benzoylamino-8-methyl-4-oxo-4H-pyrido[1,2-a]pyrimidine (**4b**).

This compound was prepared from **1b**, 6 hours of reflux, in 96% yield, mp 214-217° (from acetic acid), lit [1] mp 217.5-218.5°.

Methyl 2-Benzoylamino-3(3-benzoylamino-4-oxo-4H-pyrido[1,2-a]pyrimidinyl-9)aminopropenoate (**4f**).

This compound was prepared from **1f**, 6 hours of reflux, in 84% yield, mp 239-242° (from a mixture of ethanol and DMF); <sup>1</sup>H nmr (DMSO-d<sub>6</sub>): δ 3.74 (s, OMe), 7.31 (deg dd, H<sub>7</sub>), 7.57-7.78 (m, PhCO), 7.98-8.16 (m, PhCO, H<sub>5</sub>), 8.53 (m, H<sub>6</sub>), 8.62 (m), 8.73 (m) (H<sub>5</sub>, H<sub>9</sub>), 8.98 (d, CHNH), 9.53 (s, NHCO), 9.72 (s, H<sub>2</sub>), 11.02 (d, CHNH), H<sub>H<sub>6</sub>,H<sub>7</sub></sub> = J<sub>H<sub>7</sub>,H<sub>8</sub></sub> = 6.7 Hz; J<sub>H<sub>5</sub>,H<sub>6</sub></sub> = 6.2 Hz; J<sub>CHNH</sub> = 13.5 Hz.

Anal. Calcd. for C<sub>26</sub>H<sub>21</sub>N<sub>5</sub>O<sub>5</sub>: C, 64.59; H, 4.38; N, 14.49. Found: C, 64.91; H, 4.69; N, 14.60.

3-Benzoylamino-7-chloro-4-oxo-4H-pyrimido[1,2-b]pyridazine (**4g**).

This compound was prepared from **1g**, 4 hours of reflux, in 48% yield, mp 215° (from toluene); <sup>1</sup>H nmr (DMSO-d<sub>6</sub>): δ 7.54-8.17 (m, PhCO, H<sub>5</sub>, H<sub>9</sub>), 9.08 (s, H<sub>2</sub>), 9.75 (br s, NHCO).

Anal. Calcd. for C<sub>14</sub>H<sub>9</sub>ClN<sub>4</sub>O<sub>2</sub>: C, 55.92; H, 3.02; N, 18.63. Found: C, 55.91; H, 2.68; N, 18.47.

3-Benzoylamino-6,8-dihydroxy-4-oxo-4H-pyrimido[1,6-a]pyrimidine (**4j**).

This compound was prepared from **lj**, 5 hours of reflux, in 51% yield, mp 355-360° dec (from acetic acid); <sup>1</sup>H nmr (DMSO-d<sub>6</sub>): δ 7.49-7.93 (m, PhCO, H<sub>9</sub>), 8.53 (s, H<sub>2</sub>).

Anal. Calcd. for C<sub>14</sub>H<sub>10</sub>N<sub>4</sub>O<sub>4</sub>: C, 56.38; H, 3.38; N, 18.79. Found: C, 56.56; H, 3.41; N, 19.01.

#### 3-Benzoylamino-4-oxo-4H-pyrazino[1,2-a]pyrimidine (**4k**).

This compound was prepared from **lk**, 7 hours of reflux, in 30% yield, mp 218-221° (from toluene); <sup>1</sup>H nmr (deuteriochloroform): δ 7.27 (s, H<sub>2</sub>), 7.58-8.13 (m, PhCO, H<sub>9</sub>), 8.58 (d, H<sub>7</sub>), 9.12 (d, H<sub>6</sub>), 9.82 (s, NH).

Anal. Calcd. for C<sub>14</sub>H<sub>10</sub>N<sub>4</sub>O<sub>2</sub>: C, 63.15; H, 3.79; N, 21.04. Found: C, 63.39; H, 3.90; N, 21.04.

#### 6-Benzoylamino-4-oxo-5H-thiazolo[2,3-b]pyrimidine (**4l**).

This compound was prepared from **ll**, 3 hours of reflux, in 56% yield, mp 187-189° (from xylene), lit [1] mp 187-188°.

#### 6-Benzoylamino-3-cyano-7-oxo-1H-pyrazolo[1,5-a]pyrimidine (**4m**).

This compound was prepared from **lm**, 30 minutes of reflux, 64% yield, mp > 350° (from a mixture of ethanol and DMF); <sup>1</sup>H nmr (DMSO-d<sub>6</sub>): δ 7.48-7.57 (m) and 7.90-8.01 (m) (PhCO), 8.31 (s) and 8.50 (s) (H<sub>2</sub>, H<sub>3</sub>), 9.19 (br s, NH) (H<sub>1</sub> exchanged).

Anal. Calcd. for C<sub>14</sub>H<sub>9</sub>N<sub>5</sub>O<sub>2</sub>: C, 60.21; H, 3.25; N, 25.08. Found: C, 60.09; H, 3.39; N, 24.84.

#### 6-Benzoylamino-7-oxo-7H-1,2,4-triazolo[1,5-a]pyrimidine (**4n**).

This compound was prepared from **ln**, 5 hours of reflux, in 80% yield, mp 280° dec (from acetic acid); <sup>1</sup>H nmr (DMSO-d<sub>6</sub>): δ 7.41-7.70 (m) and 7.95-8.06 (m) (PhCO), 8.34 (s) and 8.48 (s) (H<sub>2</sub>, H<sub>3</sub>), 9.72 (s, NH).

Anal. Calcd. for C<sub>12</sub>H<sub>9</sub>N<sub>5</sub>O<sub>2</sub>: C, 56.47; H, 3.55; N, 27.44. Found: C, 56.36; H, 3.67; N, 27.46.

#### Methyl 2-Benzoylamino-3-(6-methylpyridyl-2)aminopropenoate (**3c**).

This compound was prepared from **lc**, 10 hours of reflux, in 25% yield, mp 227-230° (from xylene), <sup>1</sup>H nmr (deuteriochloroform): δ 2.51 (s, 6-Me), 3.86 (s, OMe), 6.88 (t, H<sub>4</sub>), 7.23 (s, CH), 7.41 (H<sub>3</sub>, H<sub>5</sub>), 7.49-7.86 (m, PhCO, H<sub>3</sub>, H<sub>5</sub>), 7.95 (d, CHNH), 8.40 (br d, CHNH); J<sub>CHNH</sub> = 12.5 Hz.

Anal. Calcd. for C<sub>17</sub>H<sub>17</sub>N<sub>3</sub>O<sub>3</sub>: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.40; H, 5.73; N, 13.22.

#### Methyl 2-Benzoylamino-3-(5-nitropyridyl-2)aminopropenoate (**3d**).

This compound was prepared from **ld**, 12 hours of reflux, in 35% yield, mp 203-205° (from ethanol); <sup>1</sup>H nmr (deuteriochloroform): δ 3.92 (s, OMe), 6.85 (d, CH), 7.50-7.97 (m, PhCO), 8.27-8.37 (m, H<sub>3</sub>, H<sub>4</sub>, H<sub>6</sub>), 9.15 (br d, CHNH), 11.40 (br s, NHCO), J<sub>CHNH</sub> = 13.0 Hz.

Anal. Calcd. for C<sub>16</sub>H<sub>13</sub>N<sub>4</sub>O<sub>5</sub>: C, 56.14; H, 4.12; N, 16.37. Found: C, 56.01; H, 4.31; N, 16.28.

#### Methyl 2-Benzoylamino-3-(3,5-dibromopyridyl-2)aminopropenoate (**3e**).

This compound was prepared from **le**, 8 hours of reflux, in 20% yield, mp 202-204° (from toluene); <sup>1</sup>H nmr (DMSO-d<sub>6</sub>): δ 3.76 (s, OMe), 7.49-8.08 (m, PhCO), 8.40 (m, H<sub>4</sub>, H<sub>6</sub>, CHNH), 9.05 (br s, NHCO), 9.56 (br d, CHNH), J<sub>CHNH</sub> = 12.5 Hz.

Anal. Calcd. for C<sub>16</sub>H<sub>13</sub>Br<sub>2</sub>N<sub>3</sub>O<sub>3</sub>: C, 42.23; H, 2.88; N, 9.23. Found: C, 42.60; H, 2.73; N, 9.05.

#### Methyl 2-Benzoylamino-3-(4,6-dimethylpyrimidinyl-2)aminopropenoate (**3h**).

This compound was prepared from **lh**, 7 hours of reflux, in 72% yield, mp 208-210° (from ethanol), lit [2] mp 208-210°.

#### Methyl 2-Benzoylamino-3-(2,6-dimethylpyrimidinyl-4)aminopropenoate (**3i**).

This compound was prepared from **li**, 11 hours of reflux, in 39% yield, mp 196-199° (from xylene), lit [3] mp 196-199°.

#### Methyl 2-Benzoylamino-3-(isoxazolyl-3)aminopropenoate (**3o**).

This compound was prepared from **lo**, 12 hours of reflux, in 66% yield, mp 160-161° (from toluene); <sup>1</sup>H nmr (deuteriochloroform): δ 3.66 (s, OMe), 6.37 (d, H<sub>4</sub>), 7.33-7.62 (m, PhCO), 7.96-8.08 (m, PhCO), 7.89 (d, CHNH), 8.69 (d, H<sub>3</sub>), 9.50 (d, CHNH), 9.28 (s, NHCO), J<sub>H<sub>4</sub>,H<sub>5</sub></sub> = 1.7 Hz, J<sub>CHNH</sub> = 13.4 Hz.

Anal. Calcd. for C<sub>14</sub>H<sub>13</sub>N<sub>3</sub>O<sub>4</sub>: C, 58.53; H, 4.56; N, 14.63. Found: C, 58.74; H, 4.78; N, 15.01.

#### 2-Benzoylamino-3-(5-methylisoxazolyl-3)aminopropenoate (**3p**).

This compound was prepared from **lp**, 5 hours of reflux, in 61% yield, mp 177-180° (from toluene); <sup>1</sup>H nmr (deuteriochloroform): 2.36 (d, 5-Me), 3.82 (s, OMe), 5.80 (q, H<sub>4</sub>), 7.40-7.93 (m, PhCO), 7.89 (d, CHNH), 8.35 (s, NHCO), 8.95 (d, CHNH), J<sub>H<sub>4</sub>,5-Me</sub> = 0.7 Hz, J<sub>CHNH</sub> = 10.5 Hz.

Anal. Calcd. for C<sub>15</sub>H<sub>15</sub>N<sub>3</sub>O<sub>4</sub>: C, 59.80; H, 5.02; N, 13.95. Found: C, 59.63; H, 5.03; N, 14.05.

#### 2-Phenyl-4-(5-nitro-2-pyridylamino)methylene-5(4H)-oxazolone (**5**).

A mixture of **3d** (1.71 g, 0.005 mole) and phosphorus oxychloride (1.57 g, 0.01 mole) in anhydrous pyridine (5 ml) was heated for 3 hours at 70°. The volatile components were evaporated *in vacuo*, the residue was poured on crushed ice (20 g) and the mixture was extracted with chloroform (4 times, 25 ml each time). The combined extracts were dried over anhydrous sodium sulphate, chloroform was evaporated *in vacuo* and the dry residue recrystallized from toluene to give **5** in 67% yield, mp 241-244°; <sup>1</sup>H nmr (DMSO-d<sub>6</sub>): δ 7.45 (d, CHNH), 7.63-7.97 (m, Ph), 8.04 (dd, H<sub>3</sub>), 8.57 (dd, H<sub>5</sub>), 9.18 (d, H<sub>6</sub>), 10.42 (br d, CHNH), J<sub>H<sub>3</sub>,H<sub>4</sub></sub> = 6.5 Hz; J<sub>H<sub>3</sub>,H<sub>6</sub></sub> = 1.2 Hz, J<sub>H<sub>4</sub>,H<sub>6</sub></sub> = 2.0 Hz, J<sub>CHNH</sub> = 10.5 Hz.

Anal. Calcd. for C<sub>15</sub>H<sub>10</sub>N<sub>4</sub>O<sub>4</sub>: C, 58.06; H, 3.25; N, 18.06. Found: C, 58.24; H, 3.51; N, 18.01.

#### Acknowledgement.

The authors wish to express their gratitude to the Research Council of Slovenia for partial financial support of this investigation.

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