Synthesis of Novel Derivatives of pyrano[2,3-*d*]pyrimidine*via* Intramolecular Cyclocondensation Reaction Under Acidic and Basic Conditions

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Abstract: In this study analogues of compounds based on pyrano[2,3-*d*]pyrimidine were synthesized. 1,3-dimethyl-5-(thiomethyl)-2,4,7-trioxo-1,3,4,7-tetrahydro-2H-pyrano[2,3-*d*]pyrimidine-6-carboxylic acid **3** and 1,3-dimethyl-5-(thiomethyl)-2H-pyrano[2,3-d]pyrimidine-2,4,7(1H,3H)-trione **4** were obtained by the treatment of Triethylammonium 5-[(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)(thiomethyl)methyl]-1,3-dimethylpyrimidine-2,4,6-trionate **1** with methyl sulfonic acid and pyridine, respectively. 5,5-dianilino-1,3-dimethyl-5,6-dihydro-2H-pyrano[2,3-*d*]pyrimidine-2,4,7(1H,3H)-trione **6** was obtained after oxidizing compound **4** to produce 1,3-dimethyl-5-(methylsulfinyl)-2H-pyrano[2,3-*d*]pyrimidine-2,4,7(1H,3H)-trione **5** , then the sulfoxide group on compound 5 was replaced by aniline group.

Keywords: 1,3-dimethylbarbituric acid, intramolecular cyclocondensation, meldrum's acid, pyrano[2,3-*d*]pyrimidine.

1. INTRODUCTION

Pyrimidine derivatives are known to exhibit diverse pharmacological activities as nicotinic acid receptor agonists for the treatment of dyslipidemia [1, 2], treatment of cancer and rheumatic diseases [3], through their anti-bacterial [4, 5], cardiotonic, antihypertensive [6, 7], antifungal [8], antiallergic [9], and analgesic activities [10].

The increasing interest in Pyrano[2,3-*d*]pyrimidine led to find numerous synthetic methods for preparation of this class of compounds in the literature. The methods differed intarting materials, reaction conditions and techniques. Yu *et al.* [11] reported the synthesis of pyrano[2,3-d]pyrimidine by reacting arylmethylidenemalononitrite and barbituric acid using ionic liquids as solvents. Bhuyan *et al.* [12] reacted 5-formyl-6-hydroxy uracils with meldrum's acid at reflux. Balalaie *et al.* [13] starting with aldehyde, malononitrile, barbituric acid and *L* proline as a catalyst for preparing Pyrano[2,3-d]pyrimidine *via* Domino Knoevenagel-cyclocondensation reaction. Naimi-Jamal *et al.* [14] reported a solvent-free and catalyst-free synthesis method. Bhuyan *et al.* [15] used microwave irradiation in the solid state to prepare this class of compounds.

In this study, we report the synthesis of analogue novel derivatives of pyrano[2,3-d]pyrimidine by intramolecularcyclocondensation reaction for triethylammonium 5-[(2, 2-Dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene) (thiomethyl) methyl]-1,3-dimethyl pyrimidine-2,4,6-trionate salt **1** under acidic and basic conditions.

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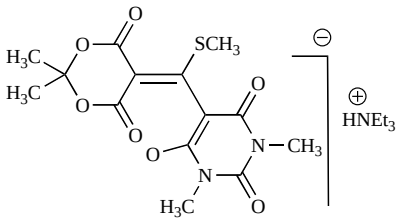
2. RESULTS AND DISCUSSION

2.1. Preparation of 1,3-dimethyl-5-(thiomethyl)-2,4,7-trioxo-1,3,4,7-tetrahydro-2H-pyrano[2,3-*d*]pyrimidine-6-Carboxylic Acid 3

The triethylammonium 5-[(2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)(thiomethyl) methyl]-1,3-dimethyl pyrimidine-2,4,6-trionate **1** have been conveniently prepared by the reaction of 5-[bis(thiomethyl)methylene] meldrum's acid **2** with 1,3-dimethylbarbituric acid in the presence of triethylamine [16].



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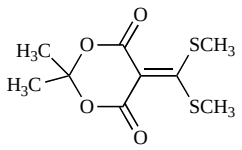

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Treating salt **1** with methylsulfonic acid at ambient conditions afforded the corresponding Intramolecular cyclization to produce **3** in good yield. Analytical data was in agreement with proposed structure. For example, unlike salt **1**, ^{1}H-NMR spectrum of **3** shows no peaks corresponding to methyl protons in meldrum's acid ring and shows a broad and short peak at 13.67 corresponding to carboxylic acid (1H, COOH). The other peaks appeared at 2.46(s,3H,SCH_3) and 3.23, 3.38 (2s, 6H, NCH_3) receptively.

The plausible reaction mechanism is an intramolecular cyclization which involves the reaction of enolate anion onbarbituric ring as nucleophile with carbonyl group onmel-

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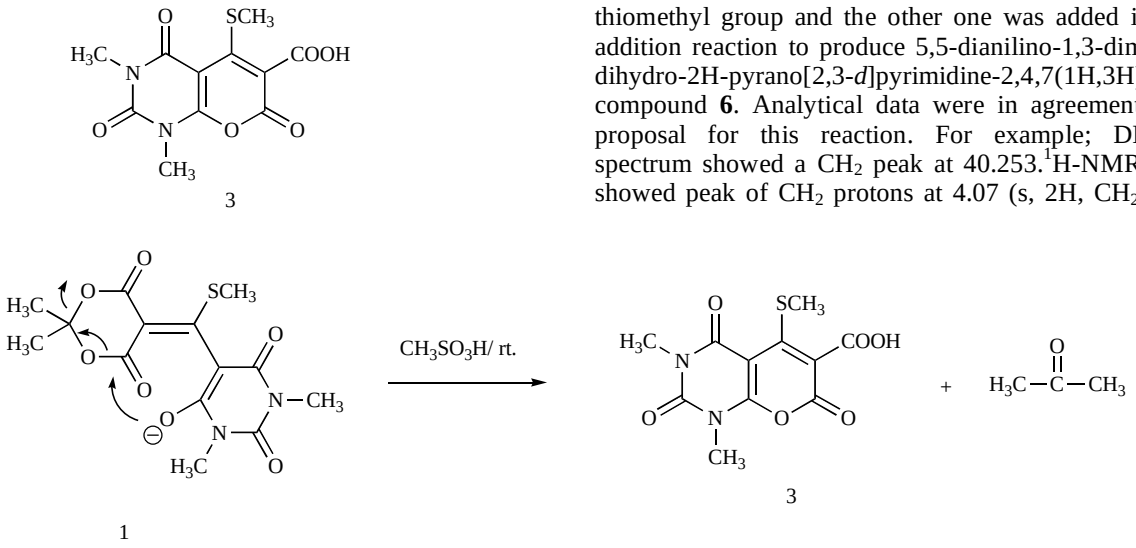

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1

3

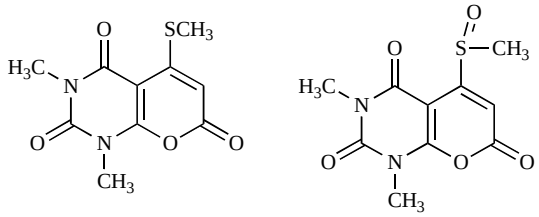
Scheme 1.

drum's acid ring to form new σ bond which is followed by the elimination of acetone (Scheme **1**).

2.2. Preparation of 1,3-dimethyl-5-(thiomethyl)-2H-pyrano[2,3-d]pyrimidine-2,4,7(1H,3H)-trione 4 and its Sulfoxide Derivative 5

Compound **1** was heated to reflux in pyridine solvent which produced 1,3-dimethyl-5-(thiomethyl)-2H-pyrano[2,3-*d*]pyrimidine-2,4,7(1H,3H)-trione **4** in good yield.

Interestingly thiomethyl group (SCH_3) could not be replaced with nucleophilic reagents such as amines [17]. In order to replace the thiomethyl group with amine it was necessary to activate the thiomethyl group. The treatment of compound **4** with *m*-chloroperbenzoic acid (MCPBA) produced compound **5** in good yield. The sulfoxidederivatives of compound **4** afforded more reactive form (compound **5**) to nucleophilic displacement reaction with amines. It is known that the nucleophilic displacement of methylsulfoxide group occurs more rapidly than the corresponding displacement of thiomethyl [18, 19]. Compound **5** can be regarded as useful intermediate for the preparation of next compound.



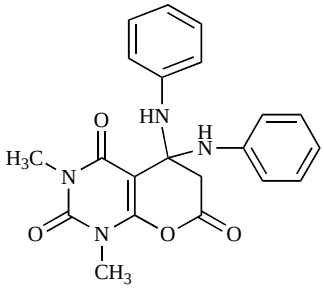
4 5

2.3. Preparation of 5,5-dianilino-1,3-dimethyl-5,6-dihydro-2H-pyrano[2,3-d]pyrimidine-2,4,7(1H,3H)-trione 6

Compound **6** could be obtained by refluxing compound **5** with aniline. The best yield could be achieved when the ratio of compound **5**:aniline is 1:2. The proposed explanation for this is that one equivalent of aniline substituted the thiomethyl group and the other one was added in Michael addition reaction to produce 5,5-dianilino-1,3-dimethyl-5,6-dihydro-2H-pyrano[2,3-*d*]pyrimidine-2,4,7(1H,3H)-trione compound **6**. Analytical data were in agreement with our proposal for this reaction. For example; DEPT-NMR spectrum showed a CH_2 peak at 40.253.^{1}H-NMR spectrum showed peak of CH_2 protons at 4.07 (s, 2H, CH_2) and aromatic protons at 7.28 – 7.54 (m, 10H, $H_{aromatic}$). The other peaks appeared at 3.13, 3.24 (2s, 6H, NCH_3) and 10.09, 14.1 (2s, 2H, NH) receptively.

3. FURTHER WORK

Pyrano[2,3-d]pyrimidine compound exhibited pharmacological activities. Our next steps will be to test compounds 3, 4, 5, and 6 for their activities. The synthesis of analogue novel derivatives of pyrano[2,3-d]pyrimidine based on compound 6 where more biologically active group will be used.



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4. EXPERIMENTAL

4.1. Materials and Instruments

All experiments have been performed in purified solvents under argon. 1,3-Dimethylbarbituric acid, Meldrum's acid, Carbon disulfide, Iodomethane, Triethylamine, Pyridine, Aniline,*m*-Chloroperbenzoic acid were purchased from Aldrich and used without further purification. Nuclear magnetic resonance (NMR) spectra were acquired by a Brucker DRX 400 NMR spectrometer with tetramethylsilane (^{1}H, ^{13}C) as external standards. Elemental analyses were determined by Carlo Erba Company, model 1106.

Triethylammonium 5-[(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)(thiomethyl) methyl]-1,3-dimethylpyrimidine-2,4,6-trionate **1** was obtained according to a published procedure [16]. 5-[bis(thiomethyl)methylene]meldrum's acid**2** was obtained according to a published procedure [20].

4.2. 1,3-dimethyl-5-(thiomethyl)-2,4,7-trioxo-1,3,4,7-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carboxylic Acid(3)

To a solution of **1** (4.58g, 10mmol) in 20 ml THF, (0.65ml, 10mmol) of methanesulfonic acid was added dropwise. The mixture was stirred at r.t. for 1 h. The THF was removed under vacuum. The residue was dissolved in 20 ml CH_2Cl_2, the solution was extracted with 10ml of water. The organic layer was dried over Na_2SO_4 and evaporated to dryness. The residue was recrystallized from dichloromethane / diethylether.

Yield: 53%; ^{1}H NMR (400.13 MHz, DMSO-d_6): 2.46(s,3H,SCH_3); 3.23, 3.38 (2s, 6H, NCH_3); 13.68 (s, 1H, COOH) ppm. ^{13}C NMR (100.62 MHz, DMSO-d_6): 16.93 (SCH_3); 28.13, 29.77 (NCH_3);92.33 ($C^5_{pyrimidine}$); 108.99 (C^3_{pyran}); 148.60 (*C*SMe); 153.7 (COOH); 156.80, 158.44, 160.08 (CO); 166.09 ($C^4_{pyrimidine}$) ppm. Anal. Calcd. for $C_{11}H_{10}N_2O_6S$: C, 44.29; H, 3.38; N, 9.39; S, 10.75. Found: C, 44.35; H, 3.77; N, 9.45; S, 10.78%.

4.3. 1,3-dimethyl-5-(thiomethyl)-2H-pyrano[2,3-d]pyrimidine-2,4,7(1H,3H)-trione (4)

(4.58, 10mmol) of **1** was heated at reflux in pyridine for 5h. The precipitate was filtered off, washed with distilled water and dried under vacuum. The residue was recrystallized from dichloromethane / diethylether.

Yield: 67%; ^{1}H NMR (400.13 MHz, CD_2Cl_2): 2.31(s,3H,SCH_3); 3.26, 3.46 (2s, 6H, NCH_3); 5.56 (s, 1H, C=CH) ppm. ^{13}C NMR (100.62 MHz, DMSO-d_6): 15.95 (SCH_3); 28.52, 29.83 (NCH_3); 96.47 ($C^5_{pyrimidine}$); 150.0 (*C*SMe); 156.0, 159.0, 160.0 (CO); 164.0 ($C^4_{pyrimidine}$) ppm.. Anal. Calcd. for $C_{10}H_{10}N_2O_4S$: C, 47.24; H, 3.96; N,11.02; S, 12.61. Found: C, 46.73; H, 4.08; N, 11.11; S, 12.96%.

4.4. 1,3-dimethyl-5-(methylsulfinyl)-2H-pyrano[2,3-d]pyrimidine-2,4,7(1H,3H)-trione (5)

To a solution of **4**(2.6, 10 mmol) in 20 ml CH_2Cl_2, (1.73, 10mmol) of *m*-chloroperbenzoic acid was added at -60°C. The mixture was stirred overnight. The CH_2Cl_2 was removed under vaccum. The residue was stirred in 20 ml diehylether for 5 minutes. The precipitate was filtered off and dried under vacuum.The residue was recrystallized from dichloromethane / diethylether.

Yield: 58%; ^{1}H NMR (400.13 MHz, CD_2Cl_2): 2.78(s,3H,S(O)CH3); 3.31, 3.53 (2s, 6H, NCH_3); 6.66 (s, 1H, C=CH) ppm. ^{13}C NMR (100.62 MHz, DMSO-d_6): 30.21, 31.64 (NCH_3); 44.80($S(O)CH_3$); 104.0 ($C^5_{pyrimidine}$); 151.12 ($\underline{C}SCH_3$); 157.26, 160.18 (CO); 170.41 ($C^4_{pyrimidine}$) ppm. Anal. Calcd. for $C_{10}H_{10}N_2O_5S$: C, 44.44; H, 3.72; N,10.37; S, 11.85. Found: C, 44.29; H, 3.72; N, 10.37; S, 11.65%.

4.5. 5,5-dianilino-1,3-dimethyl-5,6-dihydro-2H-pyrano[2,3-d]pyrimidine-2,4,7(1H,3H)-trione(6)

(2.55g,10 mmol) of **1** and (2.3m, 25mmol) of aniline were heated at reflux in 20 ml ethanol for 8h. The ethanol was removed under vacuum. The residue was recrystallized from dichloromethane / diethylether.

Yield: 54%; ^{1}H NMR (400.13 MHz, CD_2Cl_2): 2.78(s,3H,$S(O)CH_3$); 3.13, 3.24 (2s, 6H, NCH_3); 4.07 (s, 2H, CH_2); 7.28 – 7.54 (m, 10H, $H_{aromatic}$); 10.09, 14.1 (2s, 2H, NH) ppm. ^{13}C NMR (100.62 MHz, DMSO-d_6): 27.9, 28.0 (NCH_3); 40.22(CH_2); 91.0 ($C^5_{pyrimidine}$); 119.83 – 137.0 ($H_{aromatic}$); 163.68, 164.98, 168. (CO); 168.3 ($C^4_{pyrimidine}$) ppm. Anal. Calcd. for $C_{21}H_{20}N_4O_4$: C, 64.28; H, 5.14; N,14.28; S, 11.85. Found: C, 63.94; H, 5.63; N, 14.19%.

5. ACKNOWLEDGEMENTS

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CONFLICT OF INTEREST

Declared none.

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