One-pot Four Component Reaction of Unsymmetrical 1-Methylbarbituric Acid with BrCN and Various Aldehydes in the Presence of Et$_3$N and/or Pyridine

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(Received May 29, 2011; Accepted August 4, 2011)

ABSTRACT. Reaction of 1-methylpyrimidine-(1$H$,3$H$,5$H$)-2,4,6-trione (1-MBA) as an unsymmetrical barbituric acid with cyanogen bromide and various aldehydes in the presence of triethylamine and/or pyridine afforded diastereomeric mixtures of new class of heterocyclic stable 5-aryl-1,1'-dimethyl- and 5-aryl-3,1'-dimethyl-1$H$,1$H'$-spiro[furo[2,3-d]pyrimidine-6,5'-pyrimidine]2,2',4,4',6'(3$H$,3$H',5H$)-pentaones which are dimeric forms of 1-methyl barbiturate at the range of 0°C to room temperature. In the reaction of some aldehydes with 1-MBA and BrCN were afforded a mixture of diastereomers. Another two aldehydes such as 4-cyano- and 2-hydroxybenzaldehydes gave exclusively two diastereomers in which binded to the salt of triethylammonium hydrobromide by intermolecular H-bond in ratio of 1:1. 4-Hydroxybenzaldehyde and 2-pyridine-carbaldehyde gave exclusively one diastereomer under the same condition. Aldehydes possessing strong electron-donor were produced exclusively two geometric isomers of Knoevenagel adduct (E- and Z-isomers). The structures of compounds were deduced by $^1$H NMR, $^{13}$C NMR and FT-IR spectroscopy. Mechanism of the formation is discussed.

Key words: 1-Methyl barbituric acid, Spiro barbiturate, Biological effect, Cyanogen bromide, Diastereomer

INTRODUCTION

Many of heterocyclic furo[2,3-d]pyrimidines, spirobarbituric acids and fused uracils are well known as wide varieties of pharmaceutical and biological effects.

Barbituric acid reacted with cyanogen bromide in the presence of pyridine derivatives as König reaction. In this reaction, the pyridine derivative reacts with cyanogen bromide and is afterwards coupled with an active methylene to give a polymethylene dye. For example; determinations of nikethamide and niacinamide by the reaction of barbituric acid and cyanogen bromide have been used. Barbituric acids and their 2-thio analogues, both substituted and unsubstituted at nitrogens, were most often studied as C-nucleophiles of pyrimidine character. Their reaction with carbonyl compounds, with aromatic or aliphatic aldehydes gives rise to 5-aryl or 5-alkylmethylenebarbituric acids commonly in a high yield. Barbituric acids and cyanogen bromide have been used. Barbituric acids and their 2-thio analogues, both substituted and unsubstituted at nitrogens, were most often studied as C-nucleophiles of pyrimidine character. Their reaction with carbonyl compounds, with aromatic or aliphatic aldehydes gives rise to 5-aryl or 5-alkylmethylenebarbituric acids commonly in a high yield. Barbituric acids and cyanogen bromide have been used. Barbituric acids and their 2-thio analogues, both substituted and unsubstituted at nitrogens, were most often studied as C-nucleophiles of pyrimidine character. Their reaction with carbonyl compounds, with aromatic or aliphatic aldehydes gives rise to 5-aryl or 5-alkylmethylenebarbituric acids commonly in a high yield.

On the other hand, although the cyanogen bromide is toxic but it is very useful reagent in organic synthesis. It is a capable reagent for the synthesis of cyanamides, cyanates, and also used to selective cleavage of the methionyl peptide bonds in ribonuclease and etc. Nonetheless, there is no report about the reaction of 1-methylbarbituric acid (1-MBA) as an unsymmetrical barbituric acid with cyanogen bromide and aldehydes in the literature. Based on these concepts, in this research, we have investigated the one-pot reaction of 1-MBA with cyanogen bromide and various aldehydes in the presence of triethylamine and/or pyridine.

RESULTS AND DISCUSSION

Herein, we describes the new one-pot reaction of 1-methyl...
barbituric acid (1) as an unsymmetrical barbituric acid with cyanogen bromide and various aldehydes in the presence of Et$_3$N and/or pyridine afforded diastereomeric mixtures of new class of stable heterocyclic spiro barbiturates (Scheme 1). Representatively, the reaction of 1 with cyanogen bromide and benzaldehyde (2a) in the presence of triethylamine and/or pyridine in methanol afforded the salt of triethylammonium-5-bromo-2,4,6-trioxohexahydro-1-methylpyrimidin-5-ide (3) and/or pyridinium 5-bromo-1-methyl-2,4,6-trioxohexahydropyrimidin-5-ide (4), respectively and diastereomeric mixtures maximum of four new class of heterocyclic stable compounds (5S,5'S)-1',1'-dimethyl- (5a), (5S,5'S)-1',3-dimethyl- (7a) and (5S,5'R)-1',3-dimethyl-5-phenoxy-1H,1'H-spiro[furo[2,3-d]pyrimidine-6,5'-pyrimidine]-2,2',4,4',6'(3H,3'H,5H)-pentaone (8a) in good yield, respectively (and also their corresponding four enantiomers) (Scheme 1).

As a part of our current studies on barbituric acids and its reaction with cyanogen bromide and benzaldehyde (2a) in the presence of triethylamine and/or pyridine in methanol afforded the salt of triethylammonium-5-bromo-2,4,6-trioxohexahydro-1-methylpyrimidin-5-ide (3) and/or pyridinium 5-bromo-1-methyl-2,4,6-trioxohexahydropyrimidin-5-ide (4), respectively and diastereomeric mixtures maximum of four new class of heterocyclic stable compounds (5S,5'S)-1',1'-dimethyl-(5a), (5S,5'S)-1',3-dimethyl-(7a) and (5S,5'R)-1',3-dimethyl-5-phenoxy-1H,1'H-spiro[furo[2,3-d]pyrimidine-6,5'-pyrimidine]-2,2',4,4',6'(3H,3'H,5H)-pentaone (8a) in good yield, respectively (and also their corresponding four enantiomers) (Scheme 1).

On the basis of the well established chemistry of barbituric acid\textsuperscript{35} it is reasonable to assume that the enol form of 1 reacts directly with cyanogen bromide to form intermediate A through intermediates triethylammonium-2,4,6-trioxohexahydro-1-methylpyrimidin-5-ide (9) and/or pyridinium-2,4,6-trioxohexahydro-1-methylpyrimidin-5-ide (10) (path a). Intramolecular rearrangement of this intermediate produces 5-bromo-1-methylpyrimidine-(1H, 3H,5H)-2,4,6-trione (11) followed by loss of HCN to form the salts of 3 and/or 4 (obtained from triethylamine and pyridine as a base, respectively) according to similar bromination of 1-alkyl-imidazoles with BrCN\textsuperscript{29} and bromination of symmetric (thio)barbituric acids.\textsuperscript{32,33} No 1-methyl-
2,4,6-trioxohexahydopyrimidine-5-carbonitrile (12) and the salts of triethylammonium-5-cyano-2,4,6-trioxohydro-1-methylpyrimidin-5-ide (13) and/or pyridinium-5-cyano-1-methyl-2,4,6-trioxohydroxypropimidin-5-ide (14) were observed (path b) (Scheme 2). The salt of triethylammonium hydrobromide was also observed. Unfortunately, all attempts failed to separate or characterize 9 and 11. In contrast, the intermediate salt of 10 was trapped as a pink solid precipitate, separated and characterized (Its lifetime is about five minutes in the solution of reaction mixture and to be disappeared after formation during five minutes). $^1$H NMR spectrum of 10 shows a singlet at $\delta$ 2.06 ppm and a multiplet at the range of 2.94-3.13 ppm correspond to C5-H and methyl groups on barbituric acid ring moiety of the equilibrium mixture of $10A-E$ tautomers, respectively (Fig. 1a). The $^{13}$C NMR spectrum of 10 indicated the existence of at least four tautomers and show four distinct peaks for methyl group on barbituric acid ring moiety in aliphatic region (Fig. 1b). This compound shows an equilibrium mixture of different tautomers (at least four tautomers) (Scheme 3). The isolation and characterization of 10 confirms that it is an intermediate for the formation of 4 and also confirms the proposed mechanism in (Scheme 2).

The proposed mechanism for the formation of possible four diastereomers 5-8 is shown in Scheme 4. First, the Knoevenagel condensation$^{16,17}$ of 1 as an unsymmetric barbituric acid with aldehyde was afforded two geometric

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E-(15) and Z-isomers (16). Michael addition of 3 and/or 4 to 15 and 16 obtained intermediates 17-24, respectively. Unfortunately, all attempts failed to separate or characterize these intermediates (17-24). Finally, intramolecular nucleophilic attack of oxygen anion to the carbon atom (O-attack) afforded 5-8 in good yield. In this reaction, the salts of 3 and/or 4 and triethylammonium hydrobromide were also obtained (Schemes 1 and 4). 5-Bromo barbituric acids such as 5-bromo-1,3-dimethylpyrimidine-(1H, 3H,5H)-2,4,6-trione, 28 (in Fig. 4) have been reacted with unsaturated carbon-carbon double bond and formed 5-spirobarbiturate system under basic condition.$^{22,36}$

Aldehydes possessing strong electron-donor substituents in the reaction with 1 and BrCN in basic media typically afforded only Knoevenagel products 15 and 16. We performed this reaction with 4-dimethylamino benzaldehyde (2n) and anthracen-9-carbaldehyde (2r) under the same condition and the corresponding Knoevenagel con-
densation products only were found (the mixture of geometric isomers 15 and 16). The reason of this, was arose from decreasing the Lewis acidity of vinyl group in 15 and/or 16 by strong electron donor ability of substituent (Scheme 5). However, no explanation was offered for the production of spiro adduct in 3,4,5-trimethoxybenzaldehyde (2k) case.

The reaction of various aldehydes with 1 and cyanogen bromide afforded the racemic mixture of diastereomers 5-8 (consists of eight stereoisomers). The carbon atoms C5 and C6 are of chiral centre and were assigned with asterisk in the formula structures of 5-8 (Scheme 1). The separation of each diastereomer from diastereomeric mixture was unsuccessful. The structures of diastereomeric mixture of 5-8 were characterized by their IR, $^1$H NMR, $^{13}$C NMR spectra (see experimental). Representatively, the $^1$H NMR spectrum of the diastereomeric mixtures of 5a-8a consists of at least three singlets at the range of $\delta$ 4-5 ppm for methine hydrogen on C5. This observation revealed that there are three diastereomers were formed with judging to appearance of a singlet for C5-H in each isomer (The C5-H show a singlet in the similar spiro compounds derived from symmetric (thio)barbituric acids$^{32}$) (Scheme 1 and Fig. 2). At least, three singlets at $\delta$ 4.96, 4.92 and 4.87 ppm with integration ratio of 1.0:4.4:2.8 were found and corresponded to three diastereomers among of 5a-8a (Fig. 2a). In the reaction of 2k three diastereomers were found and corresponding C5-H peaks were observed at $\delta$ 4.88, 4.85 and 4.83 ppm (Fig. 2b) and obviously, three distinct diastereomers also were obtained from the reaction of 2m under the same condition (Fig. 2c). In the reaction of 2f, exclusively one distinct diastereomer was obtained (Fig. 2d). It seems the formation of diastereomers is not equal in 5a-8a, 5k-8k and 5m-8m as representative (Fig. 2). All attempts failed in results for the separation of each diastereomer due to their equal polarity, approximately by means of high performance liquid chromatography (HPLC) (Fig. 3). Nonetheless, the identification and clarification of each peak to corresponding diastereomeric structure was unsuccessful.

Barbituric acids and their 2-thio analogs, both substituted and unsubstituted at nitrogens, were most often studied as C-nucleophiles of pyrimidine character. Their reaction with carbonyl compounds, with aromatic or aliphatic aldehydes gives rise to 5-aryl or 5-alkylmethylene barbituric acids in the absence of cyanogen bromide.$^{17}$ Barbituric acids also give mono- and bis-condensation products with aldehydes.$^{38,42}$ Therefore, according to Scheme 2, the cyanogen bromide plays a major role in these reactions$^{12,33}$ through intermediate A and 11 to form 3 and/or 4. We believe that the compound 3 and/or 4 is the key reactant for the synthesis of 5-8. No 3, 4 and 5-8 were observed in the absence of cyanogen bromide under the same condition. The experimental results indicated that the yield of reaction in the presence of pyridine is higher than that of triethylamine. In comparison, the reactivity of aromatic aldehydes turned out to be higher than that of aliphatics. Also, the aromatic aldehydes possessing electron-
withdrawing substituent are more reactive than that of electron-donating substituent. Owing to the aromatic nature of BA (25) the nucleophile ability of 25 is less than that of DMBA (26) due to amide resonance dominates over the aromaticity in barbituric acids. Therefore, the nucleophilicity and reactivity of 1 is more than 25 and less than that of 26. The structures of (thio)barbituric acids (25-27) and their some derivatives (28-31) are shown in Fig. 4.

More recently, we have investigated the reaction of symmetric barbituric acids 25-27 with cyanogen bromide and various aldehydes and ketones in the presence of Et₃N. It has been found that the salts of 29-31, 5-alkyl-
and/or 5-aryl spiro[furo[2,3-d]pyrimidine-6,5'-pyrimidine][2, 2',4,4',6(3H,3'H,5H)-pentaones (dimeric forms of barbiturate, 35a'-c')\(^2\) were formed in the reaction of 25-27 with aldehydes in the presence of cyanogen bromide and triethylamine (Fig. 4). And of trimeric form of barbiturate, 5,6-dihydro-1,3-dimethyl-5,6-bis-[1',3'-dimethyl-2',4',6'-trio xo-pyrimid(5',5')yl]uro[2,3-d]uracil (33) derived from DMBA 26 in the reaction with ketone in the presence of cyanogen bromide and triethylamine by new chemical method\(^33\). Dryhurst \textit{et al.} reported the synthesis of 33 by electrochemical method\(^33\). We also reported the crystal structure of dimeric barbiturate form (32) derived from the reaction of 26 with acetone in the presence of cyanogen bromide and triethylamine\(^33,34\). Previously, the trimeric form of indandione (34) has also been reported by Barba \textit{et al.} by cathodic reduction of 2,2-dibromo-1,3-indandione in dichloromethane-Bu\(_4\)NBF\(_4\).\(^46\) In contrast, in comparison of the reactivity of 1 with 26, in the present research, no trimeric diastereomers of 36-41 (possible trimeric model forms of 1) were found from the reaction of 1 with cyanogen bromide and triethylamine and/or pyridine under the same condition (\textit{Scheme} 6 and Fig. 5).

Our observations indicated that the salt of 31 plays a major role\(^33\) and its nucleophilicity is stronger than that of 3 (this aspect is similar to the property of the salt with pyridinium moiety, 4). The salt of 3 has semi-aromatic nature with tautomerization of the proton on nitrogen atom with two neighbor’s carbonyl groups while 31 have not. The nucleophilicity should be decreased due to aromatic nature of pyrimidine ring moiety (\textit{Scheme} 7).\(^21,32,33\)

One of the most interesting phenomenons in this research is the binding of triethylammonium hydrobromide salt to some obtained spiro compounds derived from 2c, 2d, 2e and 2h by intermolecular H-bonding in ratio of 1:1. The \(^1\)H NMR spectra confirms the binding of triethylammonium hydrobromide salt to these spiro compounds. Representatively, this phenomenon is shown for spiro compounds derived from 2h in Fig. 6. First, one can unambiguously think that the salt of triethylammonium hydrobromide is of impurity into spiro compound therefore it was washed with methanol and then consequently with water twice. The mother liquid did not show the salt of triethylammonium hydrobromide. The \(^1\)H and \(^13\)C NMR spectra of spiro

\textit{Scheme} 6. No trimeric forms of 1-MBA 1 (36-41) were found in the reaction with BrCN in comparison with DMBA 26.\(^33\)

\textit{Scheme} 7. Possible tautomeric and mesomeric forms of 3, 4 and 29-31.\(^32,33\)

\textit{Fig.} 5. Possible trimeric model diastereomers of 1.
compounds derived from 2h are shown in Figs. 6 and 7, respectively. Figs. 6 and 7 indicates the formation of only two diastereomers equals in ratio, approximately assigned with A and A'). Fig. 6 also indicated the binding of triethylammonium hydrobromide salt to both diastereomers (integration ratio of C5-H and C5'-H to methyl protons on triethylammonium moiety is 0.92:9.0, respectively). Surprisingly, in the reaction of 4-hydroxybenzaldehyde (2f) and 2-pyridinecarbaldehyde (2q) with 1 and cyanogen bromide in the presence of triethylamine and/or pyridine exclusively were obtained one distinct diastereomer under the same condition! No triethylammonium hydrobromide salt was binded to these spiro compounds (Fig. 8 and see experimental section). However, no explanation was offered for this case. On the other hand, other spiro compounds did not show these behaviors.

The reaction of 2c, 2d, 2e and 2f with 1 in the presence of BrCN and triethylamine is shown in Scheme 8. In the reaction of 2c with 1 the Knoevenagel condensation and consequently Michael adduct of 6-hydroxy-5-((6-hydroxy-1-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)(2-nitrophenyl)methyl)-3-methylpyrimidine-2,4(1H,3H)-dione (42c) exclusively were found (yield 100%). The reaction of 4-cyanobenzaldehyde (2d) with 1 were afforded exclusively one diastereomer as a minor product (spiro compound assigned with B in Fig. 9, 34%) and also Michael adduct of 4-((6-hydroxy-1-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)(2-nitrophenyl)methyl)-3-methylpyrimidine-2,4(1H,3H)-dione (42c) exclusively were found (yield 100%). The reaction of 4-cyanobenzaldehyde (2d) with 1 were afforded exclusively one diastereomer as a minor product (spiro compound assigned with B in Fig. 9, 34%) and also Michael adduct of 4-((6-hydroxy-1-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)(2-nitrophenyl)methyl)-3-methylpyrimidine-2,4(1H,3H)-dione (42c) exclusively were found (yield 100%). The reaction of 4-cyanobenzaldehyde (2d) with 1 were afforded exclusively one diastereomer as a minor product (spiro compound assigned with B in Fig. 9, 34%) and also Michael adduct of 4-((6-hydroxy-1-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)(2-nitrophenyl)methyl)-3-methylpyrimidine-2,4(1H,3H)-dione (42c) exclusively were found (yield 100%). The reaction of 4-cyanobenzaldehyde (2d) with 1 were afforded exclusively one diastereomer as a minor product (spiro compound assigned with B in Fig. 9, 34%) and also Michael adduct of 4-((6-hydroxy-1-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)(2-nitrophenyl)methyl)-3-methylpyrimidine-2,4(1H,3H)-dione (42c) exclusively were found (yield 100%). The reaction of 4-cyanobenzaldehyde (2d) with 1 were afforded exclusively one diastereomer as a minor product (spiro compound assigned with B in Fig. 9, 34%) and also Michael adduct of 4-((6-hydroxy-1-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)(2-nitrophenyl)methyl)-3-methylpyrimidine-2,4(1H,3H)-dione (42c) exclusively were found (yield 100%). The reaction of 4-cyanobenzaldehyde (2d) with 1 were afforded exclusively one diastereomer as a minor product (spiro compound assigned with B in Fig. 9, 34%) and also Michael adduct of 4-((6-hydroxy-1-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)(2-nitrophenyl)methyl)-3-methylpyrimidine-2,4(1H,3H)-dione (42c) exclusively were found (yield 100%). The reaction of 4-cyanobenzaldehyde (2d) with 1 were afforded exclusively one diastereomer as a minor product (spiro compound assigned with B in Fig. 9, 34%) and also Michael adduct of 4-((6-hydroxy-1-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)(2-nitrophenyl)methyl)-3-methylpyrimidine-2,4(1H,3H)-dione (42c) exclusively were found (yield 100%).
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rahydropyrimidin-5-yl)(6-hydroxy-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)methyl)benzonitrile (42d) as a major product (66%) under the same condition (Scheme 8). The reaction of 4-bromobenzaldehyde (2e) with 1 were obtained spiro compound (70% exclusively one diastereomer) in which binded to triethylammonium hydrobromide salt in ratio of 1:1 and other Michael adduct as a minor product, 5-((4-bromophenyl)(6-hydroxy-1-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)methyl)-6-hydroxy-3-methylpyrimidine-2,4(1H,3H)-dione (42e), 30% under the same condition (Scheme 8). All these obtained results are summarized in Table 1. It seems that it has a correlation between substituent effect and reaction pathway. Aldehydes possessing of strong electron-donating substituents typically afford Knoevenagel products then consequently followed spiro compounds while possessing of strong electron-withdrawing substituents obtain Michael adduct\(^\text{37}\) (42c, 100% versus 42f, 0% in Scheme 8 and Table 1). The only exception being 4-nitrobenzaldehyde (2b) that afford spiro adduct. However, no explanation was offered for the production of spiro adduct in the later case.

Another most interesting phenomenon is shown in 42c that binded to triethylammonium salt moiety by intermolecular H-bonding. Surprisingly, in this compound one of exchangeable proton appeared in extra low field at \(\delta 16.2\) ppm that indicating the intramolecular H-bonding (Scheme 8 and see experimental section). The eight-membered intramolecular H-bonding was observed in 42c-d. Recently, the formation of some eight-membered intramolecular H-bonding has been reported.\(^\text{47}\)

**CONCLUSION**

In summary, the reaction of 1-MBA as an unsymmetrical BA with cyanogen bromide and various aldehydes in the presence of triethylamine was used to develop an efficient synthetic procedure to prepare new dimeric stable barbiturate diastereomers 1,1’-dimethyl- and 3,1’-dimethyl-1\(^1\)H,1\(^1\)H-spiro[furo[2,3-d]pyrimidine-6,5’-pyrimidine] 2,2’,4,4’,6(3H,3H,5H)-pentaones. The experimental results indicated that the aromatic aldehydes are more reactive than that of aliphatic. The aromatic aldehydes possessing strong electron-withdrawing substituent produced both
spiro compound(s) and Michael adduct (except 2-nitrobenzaldehyde that exclusively produced Michael adduct). Aldehydes possessing electron-donating substituent exclusively produced spiro compound(s). All the obtained spiro barbiturates were the racemic mixtures. Many of aldehydes in the reaction with 1-methyl barbituric acid and cyanogen bromide gave at least three diastereomers with exception of 4-cyanobenzaldehyde and salicylaldehyde in which gave two diastereomers. 4-Hydroxybenzaldehyde and 2-pyridinecarbaldehyde exclusively gave only one distinct diastereomer in detail. Triethylammonium salt moiety is binded to some these compounds by intermolecular H-bonding. All of Michael adducts showed eight-membered intramolecular H-bond.

**EXPERIMENTAL SECTION**

**General**

The drawing and nomenclature of compounds is proceeded by ChemBioDraw Ultra 12.0 version software. Melting points were measured with a digital melting point apparatus (Electrothermal) and were uncorrected. IR spectra were determined in the region 4000-400 cm\(^{-1}\) on a NEXUS 670 FT IR spectrometer by preparing KBr pellets. The \(^1\)H and \(^13\)C NMR spectra were recorded on Bruker 300 FT-NMR at 300 and 75 MHz, respectively (Urmia University, Urmia, Iran). \(^1\)H and \(^13\)C NMR spectra were obtained on solution in DMSO-\(d_6\) and/or CDCl\(_3\) as solvent using TMS as internal standard. The data are reported as (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet or unresolved, bs=broad singlet, coupling constant(s) in Hz, integration). All reactions were monitored by TLC with silica gel-coated plates (AcOEt:AcOH/80:20/v:v). FT-IR spectra were determined in the region 4000- 400 cm\(^{-1}\) on a NEXUS 670 FT IR spectrometer by preparing KBr pellets. The mass analysis performed using mass spectrometer (Agilent Technology (HP) type, MS Model: 5973 network Mass selective detector Electron Impact (EI) 70 eV), ion source temperature was 230 °C (Tehran University, Tehran, Iran). LC system: Agilent 1200-Series HPLC; column: Zorbax-C18; follow rate: 1 ml/min; detector: Diode Array Detector (DAD); pump: Quaternary pump; temperature fixed at 60 °C by thermostatted compartment. Compounds 1\(^{48}\) and cyanogen bromide\(^{49}\) was synthesized based on reported references. Aromatic aldehydes, triethylamine, pyridine and used solvents purchased from Merck and Aldrich without further purification.

**General Procedures for the Preparation of 5a-s through 8a-s, 15, 16 and 42**

The physical and spectral data of the selected compounds from 5a-s through 8a-s, 15, 16 and 42 are follows.

**5-Phenyl-1,1’-dimethyl-1H,1’H-spiro[furo[2,3-d]pyrimidine-6,5’-pyrimidine]-2,2’,4,4’,6’(3H,3’H,5H)-pentadione (5a-8a)**

In a 10 mL with Teflon-faced screw cap tube equipped by a magnetically stirrer, dissolved 0.06 g (0.48 mmol) cyanogen bromide (BrCN), 0.15 g (0.96 mmol) 1-methyl barbituric acid and 0.015 g (0.48 mmol) benzaldehyde in 10 mL methanol and then 0.8 mL triethylamine was added into solution at 0 °C. The reaction mixture was stirred for 3 h at 0 °C to room temperature. (Caution! The cyanogen bromide is highly toxic. Reactions should be carried out in a well-ventilated hood). The Teflon-faced screw cap tube prevented the vaporization of cyanogen bromide during the reaction time. The progression of reaction was monitored by thin layer chromatography (TLC). After a few minutes, the crystalline white solid precipitate, filtered off, washed with few mL methanol and dried. (0.12 g, 70% yield). The reaction procedure in the presence of pyridine (in place of triethylamine) was similar to triethylamine. Initially, the salt of pyridinium 1-methyl-2,4,6-trioxohexahydropyrimidin-5-ide (10) precipitated (its life time is about 5 minutes) then disappeared with dissolving in the reaction mixture progression. White solid; m.p. 210 °C (decomps.); FT-IR (KBr) 3407 (NH), 3200 (NH), 3038 (CH-ar.), 2965 (CH-aliph.), 2802 (CH-aliph.), 1707 (C=O), 1657 (C=O), 1536 (C=C), 1438, 1376 cm\(^{-1}\); \(^1\)H NMR (DMSO-\(d_6\) 300 MHz) \(\delta\) 2.49 (s, 3H, NMe), 3.32 (s, 3H, NMe, overlapped with water of DMSO), 4.87, 4.92, 4.96 (3s, 1H, 3CH-aliph.), 7.10 (m, 2H, Ph), 7.29 (m, 3H, Ph), 11.13 (s, 1H, NH), 11.90 (bs, 1H, NH); \(^13\)C NMR (DMSO-\(d_6\) 75 MHz) \(\delta\) 166.2, 164.4, 159.1, 155.0, 151.0, 149.9, 134.8, 129.0, 128.5, 127.0, 90.5, 86.2, 56.8, 29.2, 27.3.

**1-Methylpyrimidine-(1H,3H,5H)-2,4,6-trione (1)**

White solid; m.p. 132 °C; FT-IR (KBr) 3423 (NH), 3194 (NH), 3084 (CH-ar.), 2922 (CH-aliph.), 2850 (CH-aliph.), 1759 (C=O), 1687 (C=O), 1455, 1376, 1356, 1281 cm\(^{-1}\); \(^1\)H NMR (DMSO-\(d_6\) 300 MHz) \(\delta\) 3.03 (s, 3H, NMe), 2.57 (s, 2H, COCH=CO), 11.30 (s, 1H, NH); \(^13\)C NMR (DMSO-\(d_6\) 75 MHz) \(\delta\) 167.4, 166.9, 152.3, 77.7, 27.3.

**Pyridinium 1-methyl-2,4,6-trioxohexahydropyrimidin-5-ide (10)**

Violet solid, m.p. 224 °C (decomps.); FT-IR (KBr) 3437 (NH), 3093 (CH-ar.), 2965 (CH-aliph.), 2802 (CH-aliph.), 1682 (C=O), 1622 (C=C), 1563 (C=C), 1487, 1440, 1383 cm\(^{-1}\); \(^1\)H NMR (DMSO-\(d_6\) 300 MHz) \(\delta\) 2.06 (s, 1H,
5-(4-Nitrophenyl)-1,1'-dimethyl-1'H,1'H-spiro[furo-[2,3-d]pyrimidine-6,5'-pyrimidine]-2,2',4,4',6'(3H,3'H,5H)-pentaone (5f-8f)

White solid; m.p. 335 °C (decomp.); FT-IR (KBr) 3438 (OH), 3221 (NH), 3016 (CH-ar.), 2813 (CH-aliph.), 1706 (C=O), 1652 (C=O), 1517, 1447, 1374 cm⁻¹; ¹³C NMR (DMSO-d₆, 300 MHz) δ 2.40 (s, 3H, NMe), 2.80 (s, 3H, NMe), 3.00 (q, 6H, NMe), 5.11, 5.24 (2s, 1H, 2CH-aliph.), 6.74-6.84 (m, 3H, Ph), 7.04 (t, 1H, J = 6.6 Hz, Ph), 8.87 (bs, 1H, NHEt), 9.25, 9.29 (2s, 1H, 2OH), 11.11, 11.27 (2bs, 1H, 2NH); ¹³C NMR (DMSO-d₆, 75 MHz) δ 167.0, 169.0, 167.4, 166.5, 163.8, 163.7, 127.0, 124.4, 124.0, 121.0, 120.9, 109.2, 109.1, 90.3, 78.2, 54.9, 54.5, 46.0, 28.5, 28.1, 26.5, 26.4, 9.0 (mixture of two diastereomers bined to triethylammonium hydrobromide salt moiety).

5-(4-Hydroxyphenyl)-1,1'-dimethyl-1'H,1'H-spiro[furo-[2,3-d]pyrimidine-6,5'-pyrimidine]-2,2',4,4',6'(3H,3'H,5H)-pentaone (5i-8i)

Yellow solid; m.p. 268 °C (decomp.); FT-IR (KBr) 3406 (OH), 3200 (NH), 3019 (CH-ar.), 2814 (CH-aliph.), 1733 (C=O), 1707 (C=O), 1650 (C=O), 1518, 1442, 1377, 1274 cm⁻¹; ¹³C NMR (DMSO-d₆, 300 MHz) δ 2.47 (s, 3H, NMe), 3.04 (s, 3H, NMe), 4.95 (s, 1H, CH-aliph.), 7.08 (m, 2H, Ph), 7.47 (m, 2H, Ph), 10.30 (bs, 1H, NH), 11.13 (s, 1H, NH); ¹³C NMR (DMSO-d₆, 75 MHz) δ 166.1, 165.1, 164.5, 164.1, 159.1, 151.4, 151.0, 149.9, 144.7, 134.4, 131.7, 131.4, 131.2, 130.6, 129.5, 122.2, 117.7, 91.1, 90.2, 86.1, 55.6, 46.2, 32.5, 29.2, 27.4 (Mixture of one diastereomer of spiro compound (70%) and 42d (30%)).
White solid; m.p. 272 °C (decomps.); FT-IR (KBr) 3433 (NH), 3186 (NH), 3046 (CH-ar.), 2793 (CH-aliph.), 1721 (C=O), 1653 (C=O), 1515, 1378 cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz) δ 2.40 (s, 3H, NMe), 3.30 (s, 3H, NMe), 4.84 (s, 1H, CH-aliph.), 7.20 (m, 1H, Pyr.), 7.30 (m, 1H, Pyr.), 7.73 (m, 1H, Pyr.), 8.43 (s, 1H, Pyr.), 11.21 (s, 1H, NH), 11.96 (s, 1H, NH); ¹³C NMR (DMSO-d₆, 75 MHz) δ 166.3, 164.7, 164.0, 159.3, 154.8, 151.0, 150.0, 149.3, 137.3, 123.84, 123.78, 89.4, 85.3, 58.7, 29.2, 27.4 (Exclusively one diastereomer).

(E)-(15r) and (Z)-5-(Anthracen-9-ylmethylene)-1-methylpyrimidine-2,4,6(1H,3H,5H)-trione (16r)
Red solid; m.p. 303 °C (decomps.); FT-IR (KBr) 3188 (CH-ar.), 2857 (CH-aliph.), 1706 (C=O), 1675 (C=O), 1582 (C=C), 1444, 1379 cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz) δ 2.89 (s, 3H, NMe), 3.26 (s, 3H, NMe), 7.50 (t, 4H, J = 7.8 Hz, Anthranyl), 7.92 (t, 2H, J = 7.5 Hz, Anthranyl), 8.11 (d, 2H, J = 8.1 Hz, Anthranyl), 8.64 (s, 1H, Anthranyl), 9.00, 9.01 (2s, 1H, 2CH=C), 11.29 (s, 1H, NH), 11.74 (s, 1H, NH); ¹³C NMR (DMSO-d₆, 75 MHz) δ 162.6, 161.7, 160.6, 160.0, 152.4, 152.3, 151.32, 151.27, 151.0, 130.1, 129.9, 129.1, 128.3, 128.1, 128.0, 126.7, 126.0, 125.7, 28.1, 27.3 (Mixture of two Z- and E-isomers).

6-Hydroxy-5-((6-hydroxy-1-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)(2-nitrophenyl)methyl)-3-methylpyrimidine-2,4(1H,3H)-dione (42c)
White solid; m.p. 282 °C (decomps.); FT-IR (KBr) 3200 (NH), 2968 (CH-ar.), 2993 (CH-aliph.), 1690 (C=O), 1610 (C=C), 1527, 1461, 1363 cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz) δ 1.15 (t, 9H, J = 7.2 Hz, 3CH₂CH₂NH), 3.03 (s, 6H, 2NMe), 3.09 (q, 6H, J = 7.2 Hz, 3CH₂CH₂NH), 6.18 (s, 1H, CH-aliph.), 7.23 (m, 2H, Ph), 7.42 (m, 2H, Ph), 8.80 (bs, 1H, Et₃NH), 10.28 (s, 2H, 2NH), 16.20 (bs, 1H, OH); ¹³C NMR (DMSO-d₆, 75 MHz) δ 164.4, 162.6, 151.4, 150.3, 138.0, 131.1, 130.0, 126.5, 123.6, 90.4, 46.2, 30.9, 27.2, 9.1 (Triethylammonium salt moiety bound to 42c).

Acknowledgements. We gratefully acknowledge financial support by the Research Council of Urmia University (Grant Research no. #9-10523). The authors also gratefully acknowledge Prof. Dr. Dabbagh H. A. of Isfahan University of Technology (IUT) from Iran for his helpful discussion and guidance.

Supplementary data: Full characterization data of diastereomers among 5a-s through 8a-s and 15n, 15r, 16n, 16r are available.

Journal of the Korean Chemical Society
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