One-pot New Barbituric Acid Derivatives Derived from the Reaction of Barbituric Acids with BrCN and Ketones

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Reaction of cyclic β-dicarbonyl compounds such as pyrimidine-(1*H*,3*H*,5*H*)-2,4,6-trione (BA), 1,3-dimethyl pyrimidine-(1*H*,3*H*,5*H*)-2,4,6-trione (DMBA) and 2-thioxo-pyrimidine-(1*H*,3*H*,5*H*)-4,6-dione (TBA) with cyanogen bromide in acetone and 2-butanone in the presence of triethylamine afforded a new class of stable heterocyclic spiro[furo[2,3-*d*]pyrimidine-6,5′-pyrimidine]2,2′,4,4′,6′(3*H*,3′*H*,5*H*)-pentaones (dimeric forms of barbiturate) at 0 °C and ambient temperature. Structure elucidation was carried out by X-ray crystallographic, ^{1}H NMR, ^{13}C NMR, two dimensional NMR, FT-IR spectra, mass spectrometry and elemental analysis. The mechanism of product formation is discussed. The reaction of DMBA with cyanogen bromide in the presence of triethylamine also afforded trimeric form of barbiturate of uracil derivatives in good yield. The reaction of selected acyclic β-dicarbonyl compounds with cyanogen bromide in the presence of triethylamine in acetone and/or diethyl ether has also been investigated under the same condition. Diethyl malonate and ethyl cyanoacetate brominated and also ethyl acetocetate both brominated and cyanated on active methylene via cyanogen bromide.

Keywords: Barbituric acid; Teriethylammonium-5-bromo-2,4,6-trioxohexahydropyrimidin-5-ide; Uracil.

INTRODUCTION

Heterocyclic furo[2,3-*d*]pyrimidines,[1] pyrido[2,3-*d*]pyrimidines,[1f] spirobarbituric acids,[2] 5-alkylated and benzylated barbituric acids and other derivatives[3] are well known as pharmaceutical and biological effects.

The reaction of cyanogen bromide[4] with varieties of tertiary amines give *N*-cyanoammonium bromides in the von Braun reaction.[5] Reaction of barbituric acid with cyanogen bromide in the presence of pyridine derivatives is known as König reaction. In this reaction, the pyridine derivative reacts with cyanogen bromide and is afterwards coupled with an activated methylene to give a polymethine dye.[6] For example; determination of niketamide[7] and niacinamide[8] by the reaction of barbituric acid and cyanogen bromide has been used.

Barbituric acids can act as a nucleophile to attack various electrophiles e.g. carbodiimides,[9] benzophenone derivatives,[10] 2,2′-bipyridil to form 5,5′-(2-pyrilidine)bisbarbituric acid,[11] C_{60} molecules,[12] erythrolactol to obtain spiro barbituric deoxyribonucleoside[13] and to form spiro-linked condensed [1,2-*a*]quinolines.[14] Nitta[15] and co-workers recently have reported π-conjugated systems containing barbituric acid and 1,3-dimethyl barbituric acid derivatives.

Cyanogen bromide is a very useful reagent for the synthesis of cyanamides,[16] cyanates,[17] and also is utilized in a selective cleavage of the methionyl peptide bonds in ribonuclease[18] and etc. Cyanogen bromide also is a useful brominating agent such as; the bromination and cyanation of imidazoles,[19] free radical reaction with alkanes (bromination of alkanes)[20] and α-bromination of β-aminoenones.[21] Based on these concepts, we have investigated the reaction of cyclic β-dicarbonyl compounds such as barbituric, 1,3-dimethylbarbituric and thiobarbituric acid with cyanogen bromide and some ketones and also acyclic β-dicarbonyls such as diethyl malonate, ethyl cyanoecetate and ethyl acetoacetate with cyanogen bromide in the presence of triethylamine.

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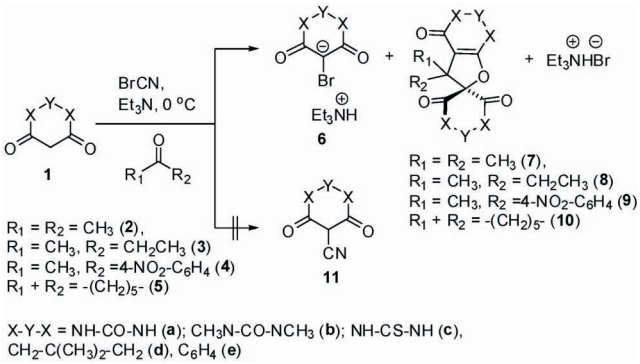
RESULTS AND DISCUSSION

Cyanogen halides such as cyanogen bromide (BrCN) like 1-cyanobenzotriazole is a convenient source of NC^+, strongly electrophilic and is a common reagent for cyanation of various compounds.[22] In this research, unsuccessful attempts were made to synthesize and isolate the 2,4,6-trioxohexahydropyrimidine-5-carbonitrile (**11a**), 1,3-dimethyl-2,4,6-trioxohexahydropyrimidine-5-carbonitrile (**11b**) and 4,6-dioxo-2-thioxohexahydropyrimidine-5-carbonitrile (**11c**). Instead, representatively, the reaction of **1a-c** with cyanogen bromide and acetone (**2**) in the presence of triethylamine afforded the salts of triethylammonium-5-bromo-2,4,6-trioxohexahydropyrimidin-5-ide (**6a**), 1,3-dimethyl triethylammonium-5-bromo-2,4,6-trioxohexahydropyrimidin-5-ide (**6b**), triethylammonium-5-bromo-4,6-dioxo-2-thioxohexahydropyrimidin-5-ide (**6c**) and a new class of stable heterocyclic compounds 5,5-dimethyl-1*H*,1′*H*-spiro[furo[2,3-*d*]pyrimidine-6,5′-pyrimidine]2,2′,4,4′,6′(3*H*,3′*H*,5*H*)-pentaone (**7a**), 1,1′,3,3′,5,5′-hexamethyl-1*H*,1′*H*-spiro[furo[2,3-*d*]pyrimidine-6,5′-pyrimidine]2,2′,4,4′,6′(3*H*,3′*H*,5*H*)-pentaone (**7b**) and 5,5-dimethyl-1*H*,1′*H*-spiro[furo[2,3-*d*]pyrimidine-6,5′-pyrimidine]2,2′-dithioxo-4,4′,6′(3*H*,3′*H*,5*H*)-trione (**7c**) in moderate yield, respectively (Scheme I).

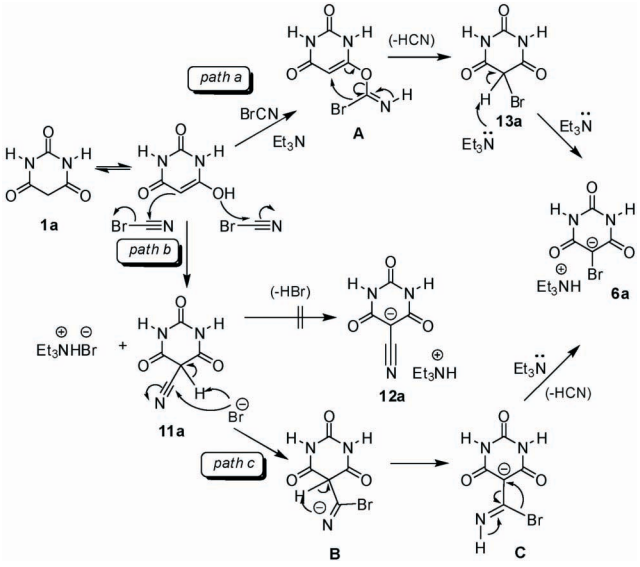
Scheme I Reaction of cyclic β-dicarbonyls (**1a-e**) with cyanogen bromide and ketones (**2-5**) in the presence of triethylamine



As a part of our current studies on barbituric acids and its reaction with cyanogen bromide and our interest in the chemistry of cyanogen bromide we discovered unexpected bromination by cyanogen bromide. The cyanation of some compounds *via* cyanogen bromide is well-known.[16,17] Here in, we report smooth bromination of barbituric acids by cyanogen bromide in the presence of triethylamine to produce the salts of **6a-c** in good yields in acetone at room temperature.

The different schematic mechanisms for the reaction between barbituric acid and cyanogen bromide are depicted in Scheme II. On the basis of the well established chemistry of barbituric acid[23] it is reasonable to assume that the enol form of barbituric acid **1a** reacts directly with cyanogen bromide to form intermediate **A** (path *a*). Intramolecular rearrangement of this intermediate produces 5-bromo-1,3-dimethylpyrimidine-(1*H*,3*H*,5*H*)-2,4,6-trione (**13a**) followed by loss of HCN, then to form the salt of triethylammonium-5-bromo-2,4,6-trioxohexahydropyrimidin-5-ide, **6a** similar to bromination of 1-alkyl-imidazoles via BrCN.[19] An alternative mechanism is presented through path *b*. In this case, the enol form of **1a** reacts directly with cyanogen bromide to form **11a**. Next, intermolecular attack by the bromide ion to nitrile group in **11a** produces intermediate **B** then intramolecularly rearrange to **C** followed by loss of HCN to form the salt of **6a** (path *c*). No triethylammonium-5-cyano-2,4,6-trioxohexahydropyrimidin-5-ide (**12a**) was observed. Therefore, it seems that the path *b* is improbable.

Scheme II Proposed mechanism for the preparation of **6a** as representative

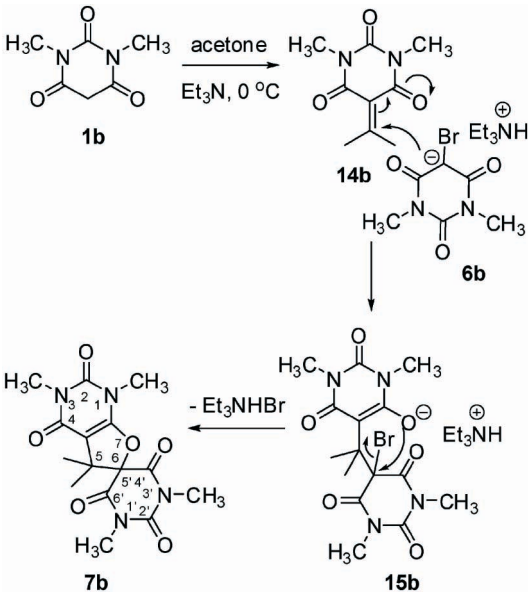


The structures of the **6a-c** were deduced by IR, ^{1}H NMR, ^{13}C NMR spectra, elemental analysis and GC-Mass spectroscopy. The ^{1}H NMR spectrum of **6a** consists of a triplet (three equivalent methyl protons at δ = 1.16 ppm), a quartet (for three equivalent methylene protons at δ = 3.08

ppm), a broad singlet (for ammonium proton at δ = 8.93 ppm) and a singlet for two equivalent amidic protons at δ = 9.38 ppm on barbituric acid ring moiety. The IR spectrum of **6a** indicated no CN bond stretching absorption. The ^{13}C NMR spectrum of **6a** shows five distinct peaks. The peak at δ = 9.09 and 46.19 ppm are of methyl and methylene carbons in triethylammonium salt moiety. The peak at 72.27 ppm corresponds to C-5 on barbituric acid ring. Two peaks at δ = 152.02 and 161.26 ppm correspond to the two unequivalent carbonyl groups on barbituric acid ring moiety, respectively (see experimental). Other evidence for the formation of **6a-c** (the existence of bromine atom in these molecules) was performed by mass analysis and also Beilstein test and the wet silver nitrate test[24] (precipitate of pale yellow silver bromide).

The proposed mechanism for the formation of **7b** is shown in Scheme III. First, the Knoevenagel condensation of **1b**[25] with acetone afforded 1,3-dimethyl-5-(propan-2-ylidene)pyrimidine-(1*H*,3*H*,5*H*)-2,4,6-trione (**14b**). Then Michael addition of 1,3-dimethyl triethylammonium-5-bromo-2,4,6-trioxohexahydropyrimidin-5-ide salt, **6b** to β-carbon position of **14b** as an α,β-unsaturated carbonyl compound gave an intermediate (**15b**). Unfortunately, all attempts failed to separate or characterize **15b**. Finally, intramolecular nucleophilic attack of oxygen anion to the carbon atom produced **7b** (moderate yield) and also triethylammonium hydrobromide salt (Scheme III). Compound **13b** was reported to react with another unsaturated carbon-carbon double bond to form 5-spirobarbiturate system under basic condition.[12,26] Attempts to synthesize **7** in acetonitrile and/or in diethyl ether gave the salts of **6** and triethylammonium hydrobromide in good yield (No **7** was observed).

Scheme III Knoevenagel condensation, Michael addition and cyclization mechanism for the formation of **7b** as representative

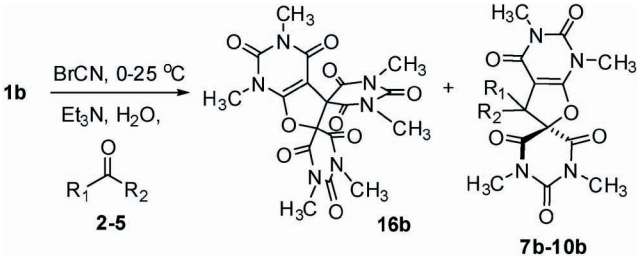


According to Scheme II, cyanogen bromide plays the major role in formation of **6** via intermediate **A** and **13**. In other words, compound **6** is the key reagent for the synthesis of **7**. No **6** and **7** were observed in the absence of cyanogen bromide under the same condition!

The structures of **7a-c** were characterized by IR, ^1H NMR, ^{13}C NMR, ^1H-^1H COSY, ^1H-^{13}C HETCOR spectra, mass analysis and X-ray crystallography (for **7b**). Recently, we have reported the crystal structure of compound **7b**[27] (Fig. 2a). ^1H-^1H COSY spectrum of **7a** shows no correlation between those three N–H signals. ^1H-^{13}C HETCOR spectrum of **7a** shows correlation of carbon signal at δ 23.75 ppm with the proton at δ 1.30 ppm which identifies the two geminal methyl protons. ^1H-^{13}C HETCOR spectrum of **7b** shows correlation of carbon signal at δ 23.33 ppm with the proton at δ 1.40 ppm. The carbon signals at δ 27.85, 29.08 and 29.63 ppm correlate with proton signals at δ 3.28, 3.36 and 3.43 ppm, respectively.

Compound 5,6-dihydro-1,3-dimethyl-5,6-bis-[1′,3′-dimethyl-2′,4′,6′-trioxo-pyrimid(5′,5′)yl]furo[2,3-*d*]uracil (**16b**) was prepared from the reaction of **1b** with cyanogen bromide and ketones **2-5** in the presence of Et_3N (a trimeric form of 1,3-dimethylbarbituric acid, Scheme IV). Previously, Dryhurst *et al* reported the synthesis of **16b** by electrochemical method.[28] Barba *et al* reported the synthesis of **16e** by cathodic reduction of 2,2-dibromo-1,3-indandione in dichloromethane-Bu_4NBF_4 (Fig. 1).[29] Here in, we report a chemical method for the synthesis of **16b** for first time.

Scheme IV Reaction of **1b** with cyanogen bromide in various ketones (**2-5**) in the presence of triethylamine for the synthesis of **16b**



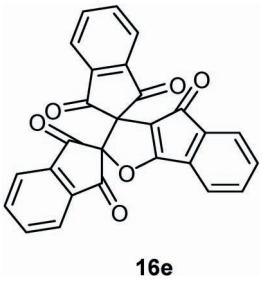
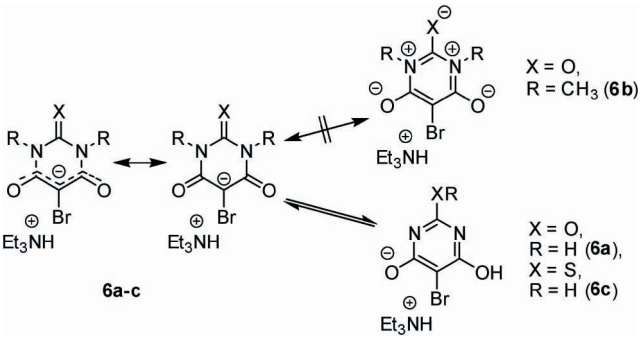


Fig. 1. Structure of **16e**.

This compound was obtained from ketone and/or another reactant containing a minimum of 5% water (water has important role in the formation of **16b**). Formation of trimeric form of 1,3-dimethyl barbituric acid (**16b**) also depends on the steric hindrance of R_1 and R_2 of the ketones. No **16a** and **16c-e** were obtained from the reaction of **1a** and **1c-e** under the same condition, respectively. These results indicate that the salt of **6b** plays an important role due to stronger nucleophilicity in compare to **6a** and **6c**. Both **6a** and **6c** have aromatic nature while **6b** does not. The aromaticity of pyrimidine ring moiety reduces the nucleophilicity (Scheme V). The ^{1}H NMR spectrum of **16b** consisted of two singlets for two unequivalent methyl groups at δ = 3.41 and 3.14 ppm, respectively, a singlet for two equivalent methyl protons at δ = 3.09 ppm and a singlet at δ = 3.02 ppm for another two equivalent methyl protons. ^{13}C NMR spectrum of **16b** consisted of fourteen distinct peaks that confirms the structure of **16b** (see experimental and Fig. 2b).

Scheme V Tautomeric and mesomeric forms of **6a-c**



The formation of the barbituric acid trimer may be involve in oxidation of the enol form and then radical coupling.[30] The proposed mechanism of the formation of **16b** by chemical method is shown in Scheme VI. The 1,3-dimethyl pyrimidine-2,4,5,6(1*H*,3*H*)-tetraone (1,3-dimethyl alloxan, **17b**) was formed from the oxidation of 1,3-dimethyl barbituric acid **1b**.[28,31] Knoevenagel condensation of **1b** with **17b** produced 1,3,1′,3′-tetramethyl-[5,5′]-bipyrimidinylidene-2,4,6,2′,4′,6′-hexaone (**18b**). Of course, the alloxan derivative can also be prepared from the oxidation of barbituric acid and its derivatives e.g. 5-hydroxy barbituric acid (HB), 5-alkylidene and/or arylidene barbituric acids.[31] The conversion of HB to alloxan by electrochemical method has also been reported.[31g] 5-Hydroxy barbituric acid can also be prepared from 5-bromo barbituric acid under alkali condition.[31h,i] α-Diketo compounds e.g. isatin has been condensed with barbituric acids by Knoevenagel condensation reaction.[32,33] Therefore, like isatin, 1,3-dimethyl alloxan, **17b** can be condensed with **1b** to obtain **18b**. The Michael addition of **6b** with **18b** formed intermediate **19b**. Then intramolecular nucleophilic attack of oxygen anion to C5 atom of barbituric acid ring moiety (pushing the bromide ion out) to form **16b** and triethylammonium hydrobromide salt (Scheme VI). Unfortu-

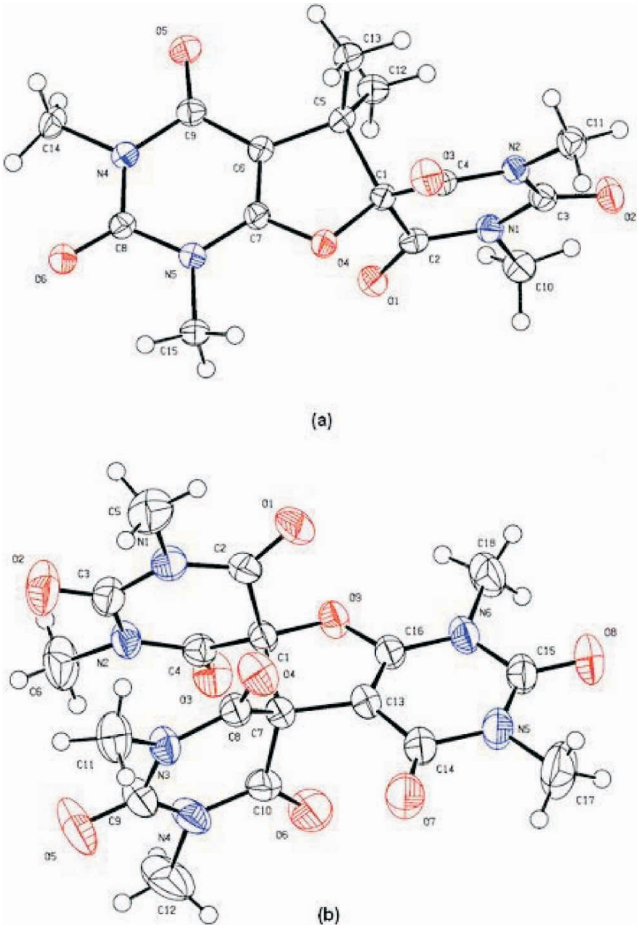
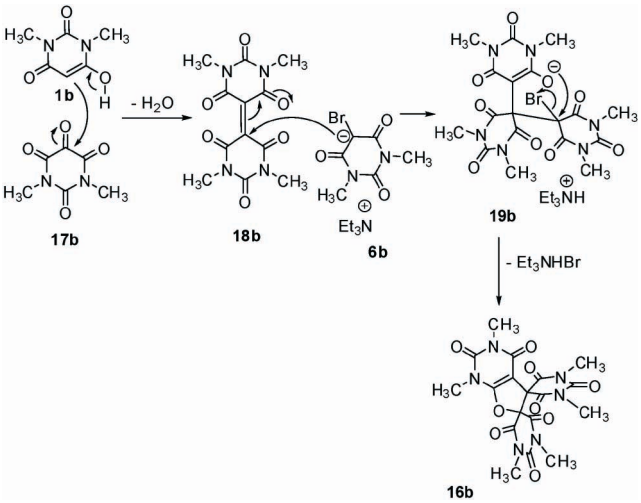


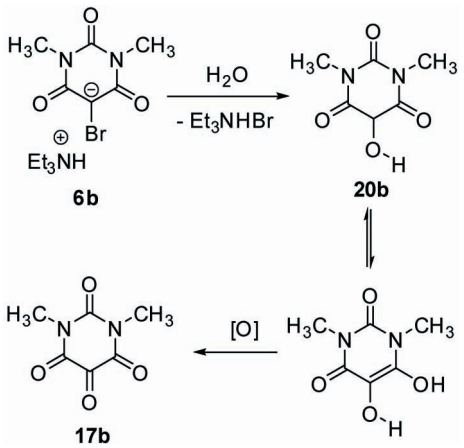
Fig. 2. X-ray crystal structure of **7b**[27] (a) and **16b** (b) synthesized by chemical method.

Scheme VI Proposed mechanism for the formation of **16b** via chemical method



nately, all attempts failed to separate and characterize **17b**, **18b** and **19b**. We concluded that 1,3-dimethyl triethylammonium-5-bromo-2,4,6-trioxohexahydropyrimidin-5-ide, **6b** was hydrolyzed to 5-hydroxy-1,3-dimethylbarbituric acid (**20b**) by the small amount of water and then oxidized to 1,3-dimethyl alloxan, **17b** (Scheme VII). We examined the reaction of **1b** in extra pure acetone (≈ 99.5 to 99.9%) under the same condition. No **16b** was observed but only **6b** and **7b** were obtained. Compounds **8a-c** and **16b** were obtained from the reaction of **1a-c** with 2-butanone (**3**) and cyanogen bromide under the same condition, respectively. In contrast, the reaction of 4-nitro acetophenone (**4**) and cyclohexanone (**5**) with **1b** only produced the trimeric form (**16b**) under the same condition. Thus, we

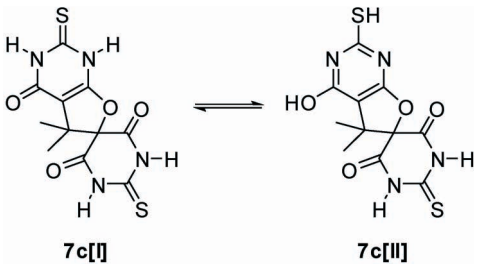
Scheme VII Proposed mechanism for the formation of 1,3-dimethyl alloxan **17b**



conclude that the existence of trace amount of water converts **6b** to **17b** through intermediate **20b** (Scheme VII). Compound **17b** is a reactive compound which easily condensed with **1b** prior to Knoevenagel condensation of **1b** with ketones **2-5** (especially with hindrance and bulky ketones such as **4** and **5**). The formation of **16b** is a competing reaction parallel with the formation of **7b** and **8b**. We performed the reaction of 5,5-dimethylcyclohexane-1,3-dione (dimedone, **1d**) and 1,3-indandion (**1e**) with cyanogen bromide in **2-5** in the presence of triethylamine under the same condition. No **7d-10d** and **7e-10e** were obtained by the chemical method.

The sulfur analogues of the compounds **7c-10c** may have two tautomeric forms. For **7c**, this phenomenon arose from the strong nucleophilicity of the sulfur in thiocarbonyl group of the thiouracil ring moiety, which tautomerized to thiol functional group [lactim-thiolactim form (**7c[II]**)] on pyrimidine ring moiety (resulting a tautomeric equilibrium mixture). In other words, a mixture of lactam-thiolactam (**7c[I]**) and lactim-thiolactim (**7c[II]**) exist in an equilibrium mixtures (Scheme VIII).[34] Another interesting observed phenomenon was the equilibrium mixture of two tautomers of **8a**. The ^{1}H and ^{13}C NMR spectra of **8a** show two distinct tautomers (existence of more than four NH peaks in ^{1}H NMR and the number of ^{13}C NMR peaks). This indicates the equilibrium mixture of lactam and lactim forms and has enough lifetimes in NMR time scale (Fig. 3).

Scheme VIII Tautomeric forms of **7c** as representative



Furthermore, the reaction of some acyclic β-dicarbonyl compounds with cyanogen bromide in acetone in the presence of triethylamine were also examined. Reaction of diethyl malonate (DEM) (**21a**), ethyl cyanoacetate (ECA) (**21b**) and ethyl acetoacetate (EAA) (**21c**) with cyanogen bromide in acetone formed diethyl bromomalonate (**22a**) and ethyl bromoacetoacetate (**22c**) in moderate yield, respectively. Triethylammonium hydrobromide salt was ob-

served in all reaction products (Schemes I and IX).

The ^{1}H NMR spectrum of diethyl bromomalonate, **22a** show a triplet at δ 1.31 and a quartet at δ 4.29 ppm are of to equivalent methyl and methylene protons, respectively. A singlet at δ 4.82 corresponds to the CHBr proton. The peak integration ratios 1.0:4.0:6.0 are of methine, two methylene and two methyl protons, respectively. These ratios are in good agreement with the structure of **22a**. The ^{13}C NMR spectrum of **22a** show a peak at δ 13.85 and 63.21 ppm are of methyl and methylene carbon atoms, at δ 42.40 and 164.58 ppm corresponds to the methine and carbonyl carbon atoms, respectively (see experimental).

Diethyl cyanomalonate, **23a** has been synthesized previously by the reaction of ethyl cyanoacetate, **21b** with

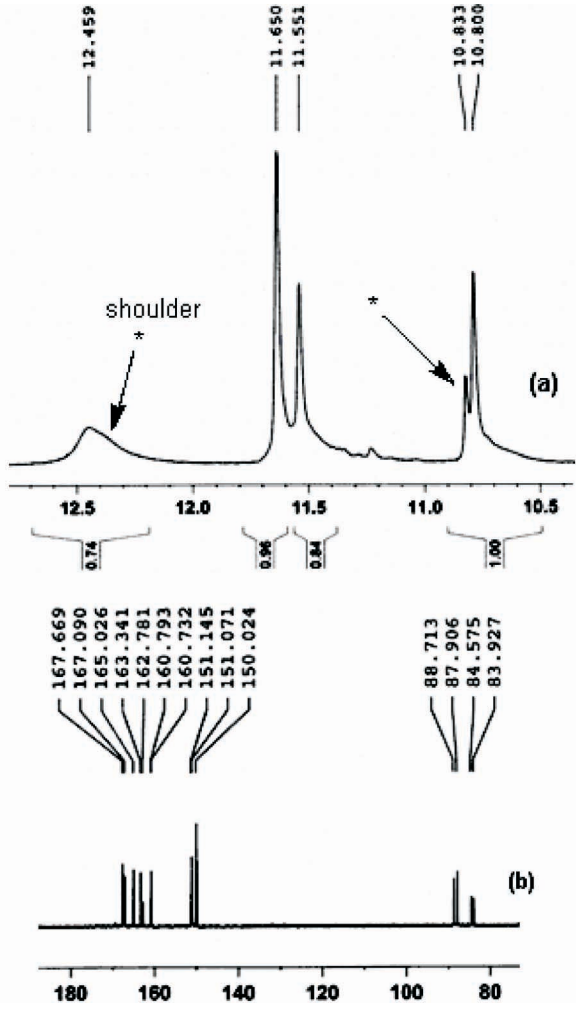
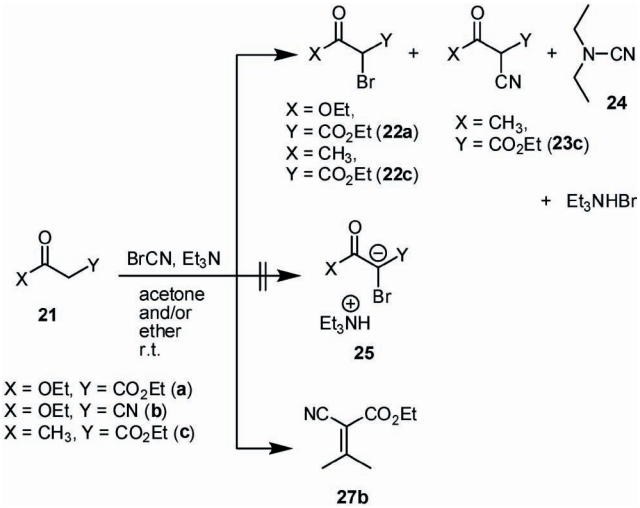


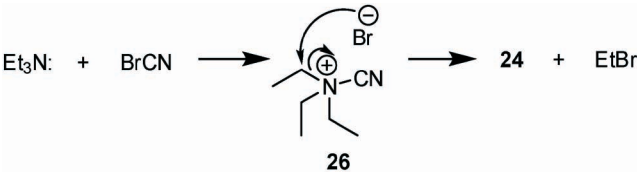
Fig. 3. The expanded ^{1}H NMR spectrum (minor tautomer is assigned by *) of the equilibrium mixtures of two lactam and lactim forms (a) and ^{13}C NMR spectrum (b) of **8a**.

Scheme IX Cyanation and bromination of **21** via cyanogen bromide and formation of **27b** from **21b**



ethyl chloroformate in the presence of anhydrous potassium carbonate in acetone.[35] We performed the reaction of **21a** with cyanogen bromide according to method of reference 35 (formation of **23a** was not observed). In contrast, our experiments indicated that the reaction of **21a** with cyanogen bromide leads to diethyl bromomalonate, **22a** and *N,N*-diethylcyanamide (**24**) in acetone and/or ether (Scheme IX). Expectedly, triethylamine attacks the NC^+ of cyanogen bromide obtaining triethylcyanoammonium bromide salt (**26**) (Scheme X). According to Scheme X, the ethyl bromide and **24** were observed based on von Braun reaction[5] through analyzing the crude reaction mixture by GC-Mass analyses.

Scheme X Formation of **24** via von Braun reaction[5]



The reaction of ethyl cyanoacetate, **21b** with cyanogen bromide in ether indicated no significant product(s). In contrast, in acetone as a polar aprotic solvent ethyl 2-isopropylidenecyanoacetate (**27b**) was afforded by means of the condensation of **21b** with acetone in 32% yield (Scheme IX). No **22b** and **23b** were observed in this reaction. The structure of **27b** was characterized by ^{1}H NMR,

^{13}C NMR and GC-Mass analysis. ^{1}H NMR spectra show two singlets at δ 2.31 and 2.41 ppm, corresponding to the two geminal methyl protons on carbon-carbon double bond. A triplet at δ 1.36 and a quartet at 4.27 ppm correspond to methyl and methylene groups, respectively. ^{13}C NMR spectrum of **27b** shows eight distinct peaks that confirms its structure characterization (see experimental).

Interestingly, ethyl bromoacetoacetate, **22c** or ethyl cyanoacetoacetate (**23c**) were found in the reaction between ethyl acetoacetate, **21c** and cyanogen bromide in ether as nonpolar aprotic solvent (Scheme IX). Some other unknown compounds also were observed as by-products by means of GC-Mass analyzing. The separation of all products released from **21c** was unsuccessful by silica gel column chromatography. No distinct product(s) were observed in acetone. We characterized the structures of **22c** and **23c** (from crude reaction mixture) by means of GC-Mass analyses. No triethylammonium 2-bromo-1,3-diethoxy-1,3-dioxopropan-2-ide (**25a**), triethylammonium 1-bromo-1-cyano-2-ethoxy-2-oxoethan-1-ide (**25b**) and triethylammonium 2-bromo-1-ethoxy-1,3-dioxobutan-2-ide (**25c**) salts were obtained in the reactions of **21a-c** with cyanogen bromide in presence of triethylamine, respectively. The results from GC-Mass analyses of the obtained products from **21a-c** were summarized in Table 1.

Table 1. The summary of GC-Mass analysis of the reaction between **21a-c** with cyanogen bromide

Compd.	Reaction Solvent	RT[a]/min	Material(s) obtained from column elution	Yield [b] (%)
21a	Ether	1.11	**24**	13.5
21a	Ether	2.32	**21a**	64.1
21a	Ether	3.64	**22a**	20.0
21a	Acetone	0.85	**24**	14.3
21a	Acetone	2.44	**21a**	47.6
21a	Acetone	3.96	**22a**	38.1
21b	Ether	1.62	**21b**	100
21b	Acetone	1.66	**21b**	39
21b	Acetone	3.17	**27**	32
21c	Ether	2.71	**21c**	11
21c	Ether	2.75	**22c**	20
21c	Ether	2.95	**23c**	10
21c	Acetone	2.56	**22c**	trace

[a] Retention time. [b] Yields refer to peak integration.

X-Ray analysis of compound 16b

Crystals of **16b** were obtained by slow evaporation of a solution of **16b** in acetone at room temperature. The data were acquired using a STOE IPDS II diffractometer, data collection and cell refinement were processed using STOE X-AREA (Stoe & Cie, 2002) and data reduction was processed using STOE X-RED (Stoe & Cie, 2002) program. Program(s) used to refine structure was *SHELXL97* (Sheldrick, 1997, University of Göttingen, Germany, 1997). Crystal data for **16b**: Orthorhombic; $C_{18}H_{18}N_6O_9$; M 462.38; Unit cell parameters at 293(2) K: a = 13.2422(4), b = 15.9176(6), c = 19.5817(6) Å; α = β = γ = 90°; V = 4127.5(2) Å^3; Z = 8; μ = 0.122 mm^{-1}; Total reflection number 4275; 304 parameters; λ = 0.71073 Å; 2916 reflections with $I > 2\sigma(I)$; R_{int} = 0.056; θ_{max} = 26.49°; $R[F2 > 2\sigma(F2)]$ = 0.048; $wR(F2)$ = 0.112; S = 1.02, F_{000} = 1920. The crystallographic data for **16b** were deposited to the Cambridge Crystallographic Data Center (entry no. CCDC-786144) and are available free of charge upon request to CCDC, 12 Union Road, Cambridge, UK (fax: +44-1223-336033, *e-mail*: *deposit@ccdc.cam.ac.uk*).

EXPERIMENTAL

General

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 in $CDCl_3$ as solvents using TMS as internal standard. Elemental analyses were performed using a VarioEL III analyzer (Tabriz University, Tabriz, Iran). 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 ºC (Tehran University, Tehran, Iran). The GC-Mass analyses were recorded on Thermo Finnigan K970 (Urmia University). The compounds **1a-c** were synthesized and purified in our laboratory as described in literature previously.[36] Cyanogen bromide was synthesized based on reported references.[4] Compounds **21a-c**, triethylamine and used solvents purchased from Merck and Aldrich without further purification.

Preparation of compound 7a

Synthetic Procedure for 5,5-dimethyl-1*H*,1′*H*-spiro[furo[2,3-*d*]pyrimidine-6,5′-pyrimidine]-2,2′,4,4′,6′(3*H*,3′*H*,5*H*)-pentaone 7a

In a round bottom flask equipped with magnetically

stirrer, 0.075 g (0.58 mmol) barbituric acid and 0.033 g (0.58 mmol) acetone were dissolved in 25 mL methanol and were refluxed for 24 h. The 0.075 g (0.58 mmol) barbituric acid and 0.1 mL (0.75 mmol) triethylamine was added into previous solution and transferred into a separatory funnel. This solution was added drop wise into the solution of 0.052 g (0.58 mmol) BrCN equipped with an ice-bath and magnetically stirrer then stirred for 3 hours. (*Caution! The cyanogen bromide is highly toxic. Reactions should be carried out in a well-ventilated hood*). Finally, the reaction mixture perturbed to dark red color. The reaction mixture was kept overnight at room temperature and white crystalline solid precipitated, filtered, washed with cold water and dried. (0.07 g, 50%), mp 165-166 °C (decomps.). FT-IR (KBr): 3523, 3245, 2848, 1708, 1655 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, δ): 1.30 (s, 6H), 10.77 (s, 1H), 11.68 (s, 2H), 12.43 (bs, 1H). ^{13}C NMR (75 MHz, DMSO-d_6, δ): 165.7, 162.5, 160.5, 151.0, 150.1, 92.6, 91.0, 50.5, 23.8. Anal. Calcd for $C_{11}H_{10}N_4O_6$ (MW 294.11): C, 44.88; H, 3.43; N, 19.05. Found: C, 41.71; H, 3.44; N, 16.70%. MS *m/z*: 294 (M^+, 21), 279 (base peak, 100), 236 (15), 219 (5), 193 (40), 167 (20), 150 (25), 122 (10), 108 (8), 82 (10), 56 (35), 44 (15).

1,1′,3,3′,5,5′-Hexamethyl-1*H*,1′*H*-spiro[furo[2,3-*d*]pyrimidine-6,5′-pyrimidine]2,2′,4,4′,6′(3*H*,3′*H*,5*H*)-pentaone 7b

White solid, mp 210-212 °C (decomps.). FT-IR (KBr) 2982, 2955, 1689, 1646 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, δ): 1.40 (s, 6H), 3.28 (s, 3H), 3.36 (s, 6H), 3.43 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6, δ): 164.3, 160.2, 158.9, 151.0, 150.2, 93.2, 91.1, 53.9, 29.6, 29.1, 27.9, 23.3. Anal. Calcd. for $C_{15}H_{18}N_4O_6$ (MW 350.33): C, 51.38; H, 5.14; N, 15.99. Found: C, 51.23; H, 5.63; N, 16.14%.

5,5-Dimethyl-1*H*,1′*H*-spiro[furo[2,3-*d*]pyrimidine-6,5′-pyrimidine]2,2′-dithioxo-4,4′,6′(3*H*,3′*H*,5*H*)-trione 7c

Pale yellow crystalline solid, mp 190 °C (decomps.). FT-IR (KBr) 3437, 2968, 1666 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, δ): 1.20 (s, 6H), 1.26 (s, 6H), 12.40 (bs, 4H), 13.32 (bs, 4H) (The mixture of two tautomers **7c[I]** and **7c[II]**). ^{13}C NMR (75 MHz, DMSO-d_6, δ): 171.9, 167.6, 162.0, 157.8, 108.4, 87.6, 85.2, 67.8, 28.8, 14.3.

Teriethylammonium-5-bromo-2,4,6-trioxohexahydropyrimidin-5-ide 6a

White solid (50%), mp 155-158 °C (decomps.). FT-IR (KBr) 3130, 2985, 1658, 524 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, δ): 1.16 (t, 9H), 3.08 (q, 6H), 8.93 (bs, 1H), 9.38 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6, δ): 161.3, 152.0, 72.3, 46.2, 9.1. Anal. Calcd. for $C_{10}H_{18}N_3O_3Br$: C, 38.9; N, 13.63; H, 5.84. Found: C, 39.04; N, 13.66; H, 5.92%. MS *m/z*: 308 (M^+, 0), 154 (7), 128 (base peak, 100), 101 (15), 86 (60), 72 (5), 58 (16), 42 (98).

Triethylammonium-1,3-dimethyl-5-bromo-2,4,6-trioxohexahydropyrimidin-5-ide 6b

White solid (45%), mp 152-154 °C (decomps.). FT-IR (KBr) 3200, 2980, 1670, 526 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, δ): 1.17 (t, 9H), 2.80 (s, 6H), 3.08 (q, 6H), 8.95 (bs, 1H). ^{13}C NMR (75 MHz, DMSO-d_6, δ): 161.9, 157.1, 73.4, 46.1, 30.2, 9.1. Anal. Calcd. for $C_{12}H_{22}N_3O_3Br$: C, 42.87; N, 12.50; H, 6.60. Found: C, 42.65; N, 12.43; H, 6.52%.

Triethylammonium-5-bromo-4,6-dioxo-2-thioxohexahydropyrimidin-5-ide 6c

White solid (50%); mp 159-161 °C. FT-IR (KBr) 3408, 2975, 1648, 1612, 590 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, δ): 1.16 (t, 9H), 3.07 (q, 6H), 10.17 (bs, 1H), 10.35 (bs, 2H). ^{13}C NMR (75 MHz, DMSO-d_6, δ): 174.7, 164.3, 79.7, 46.2, 9.1. Anal. Calcd. for $C_{10}H_{18}N_3O_2SBr$: C, 37.05; N, 12.97; H, 5.56. Found: C, 37.10; N, 13.05; H, 5.51%.

5-Ethyl-5-methyl-1*H*,1′*H*-spiro[furo[2,3-*d*]pyrimidine-6,5′-pyrimidine]2,2′,4,4′,6′(3*H*,3′*H*,5*H*)-pentaone 8a

White crystalline solid, mp 182 °C (decomps.). FT-IR (KBr) 3258, 2852, 1762, 1717, 1656 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, δ): 1.19 (t, 3H), 3.09 (m, 1H), 3.18 (s, 3H), 3.60 (q, 1H), 10.80 (s, 1H), 11.55 (s, 1H), 11.65 (s, 1H), 12.46 (bs, 1H). ^{13}C NMR (75 MHz, DMSO-d_6, δ): 167.7, 167.1, 165.0, 163.3, 162.8, 160.8, 160.7, 151.2, 151.1, 150.0, 88.7, 87.9, 84.6, 83.9, 46.2, 45.0, 35.1, 15.5, 9.1 (Mixture of two tautomers); MS *m/z*: 308 (M^+, 1), 291 (6), 277 (20), 262 (3), 248 (30), 222 (21), 206 (18), 178 (10), 163 (18), 149 (20), 135 (10), 108 (7), 93 (10), 70 (30), 44 (100).

5-Ethyl-1,1′,3,3′,5-pentamethyl-1*H*,1′*H*-spiro[furo[2,3-*d*]pyrimidine-6,5′-pyrimidine]2,2′,4,4′,6′(3*H*,3′*H*,5*H*)-pentaone 8b

White crystalline solid, mp 197 °C (decomps.). FT-IR (KBr) 2959, 1690, 1654 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, δ): 1.32 (s, 3H), 3.31 (s, 3H), 3.37 (s, 3H), 3.38 (s, 3H), 3.44 (s, 3H), 3.81 (q, 2H, J = 6.9 Hz). ^{13}C NMR (75 MHz, DMSO-d_6, δ): 165.8, 163.4, 161.1, 159.2, 151.1, 149.9, 88.9, 87.9, 66.0, 54.0, 47.8, 29.8, 29.5, 29.0, 28.0, 14.9; MS *m/z*: 364 (M^+, 1), 336 (30), 293 (10), 249 (12), 220 (30), 181 (100), 149 (35), 124 (8), 97 (5), 80 (10), 57 (15), 43 (18).

5-Ethyl-5-methyl-1*H*,1′*H*-spiro[furo[2,3-*d*]pyrimidine-6,5′-pyrimidine]2,2′-dithioxo-4,4′,6′(3*H*,3′*H*,5*H*)-trione 8c

Yellow crystalline solid, mp 204 °C (decomps.). FT-IR (KBr) 3432, 2925, 1640, 1635 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, δ): 1.15 (t, 3H), 2.50 (s, 3H), 3.06 (m, 2H), 8.85 (bs, 1H), 9.71 (bs, 1H), 10.89 (bs, 1H), 12.12 (bs, 1H). ^{13}C NMR (75 MHz, DMSO-d_6, δ): 178.0, 176.0, 168.2, 166.6, 165.6, 163.7, 90.3, 83.0, 46.2, 13.4, 9.1.

5,6-Dihydro-l,3-dimethyl-5,6-bis-[l′,3′-dimethyl-2′,4′,6′-trioxo-pyrimid(5′,5′)yl]furo[2,3-*d*]uracil 16b[28]

White solid (50%), mp 255 °C (decomps.). FT-IR (KBr) 2959, 1724, 1704, 1660 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, δ): 3.02 (s, 6H), 3.09 (s, 6H), 3.14 (s, 3H), 3.41 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6, δ): 164.2, 162.7, 161.3, 157.4, 150.8, 150.2, 150.0, 96.2, 94.3, 92.1, 30.5, 30.1, 29.6, 28.3. MS *m/z*: 462 (M^+, 3), 348 (2), 320 (7), 252 (7), 178 (3), 101 (20), 86 (100), 58 (25), 42 (10).

Diethyl bromomalonate 22a

The experimental procedure for the reaction of **21a**, **21b** and **21c** with cyanogen bromide and triethylamine in acetone, acetonitrile and ether were similar to the barbituric acid experimental procedure. Colorless oily liquid (38%). FT-IR (KBr) 2985, 1743, 1150 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, δ): 1.31 (t, 6H), 4.29 (q, 4H), 4.82 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6, δ): 164.6, 63.2, 42.4, 13.9. GC-MS *m/z*: (RT, 3.96 min.), 241 (M+2), 239 (M), 212 (2), 193 (10), 166 (18), 140 (30), 138 (42), 120 (20), 29 (100, base peak).

Ethyl 2-isopropylidenecyanoacetate 27b[37]

Colorless oily liquid (32%). FT-IR (KBr) 2976, 2237, 1735, 1476 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, δ): 1.36 (t, 3H), 2.31 (s, 3H), 2.41 (s, 3H), 4.27 (q, 2H). ^{13}C NMR (75 MHz, DMSO-d_6, δ): 173.5, 115.7, 105.0, 61.7, 46.0, 27.3, 22.8, 14.1. GC-MS *m/z*: (RT, 3.17 min.), 154 (2), 153 (14), 125 (40), 108 (63), 97 (100, base peak), 27 (64).

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