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New Strategy for the Synthesis of 5-Aryl-1*H*,1'*H*-spiro[furo[2,3-*d*]pyrimidine-6,5'-pyrimidine]2,2',4,4',6'(3*H*,3'*H*,5*H*)-pentaones and Their Sulfur Analogues

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Reaction of barbituric acid (BA), 1,3-dimethyl barbituric acid (DMBA) and 2-thiobarbituric acid (TBA) with cyanogen bromide and aldehydes in the presence of L-(+)-tartaric acid afforded a new route for the synthesis of stable heterocyclic 5-aryl-1*H*,1'*H*-spiro[furo[2,3-*d*]pyrimidine-6,5'-pyrimidine]2,2',4,4',6'(3*H*,3'*H*,5*H*)-pentaones which is a dimeric form of barbiturate (uracil and thiouracil derivative). In the reaction of 1,3-diethyl thiobarbituric acid (DETBA) the Knoevenagel condensation and then Michael adducts were obtained under the same condition. Structure elucidation is carried out by ^{1}H NMR, ^{13}C NMR, FT-IR and Mass analyses. Mechanism of the formation is discussed.

Key Words : Barbituric acid, Spiro[furo[2,3-*d*]pyrimidine-6,5'-pyrimidine]pentaone, Cyanogen bromide, Uracil, L-(+)-Tartaric acid

Introduction

Many of heterocyclic furo[2,3-*d*]pyrimidines,[1] spirobarbituric acids[2] and fused uracils[3,4] 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 polymethine dye.[5] For example; determinations of niketamide[6] and niacinamide[7] by the reaction of barbituric acid and cyanogen bromide have been used.

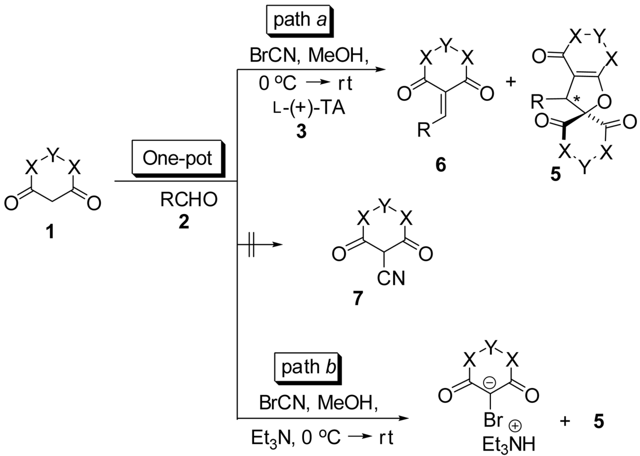
Cyanogen bromide is a very useful reagent for the synthesis of cyanamides,[8] cyanates,[9] and also is utilized in a selective cleavage of the methionyl peptide bonds in ribonuclease,[10] and etc. Cyanogen bromide also is a useful brominating agent such as; the bromination and cyanation of imidazoles[11], free radical reaction with alkanes (bromination of alkanes)[12] and α-bromination of β-aminoenones.[13]

Based on these concepts, we report the new reaction of barbituric acids with cyanogen bromide and various aldehydes in the presence of L-(+)-tartaric acid.

Results and Discussion

This paper describes the new reaction of barbituric acids with cyanogen bromide and aldehydes in the presence of L-(+)-tartaric acid to afford a class of stable heterocyclic spiro barbiturate compounds. Representatively, the reaction of BA (**1a'**), DMBA (**1b'**) and TBA (**1c'**) with cyanogen bromide and benzaldehyde (**2a**) in the presence of L-(+)-tartaric acid in methanol afforded new class of stable heterocyclic compounds 5-phenyl-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 (**5aa'**), 5-phenyl-1,1',3,3'-tetramethyl-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 (**5ab'**) and 5-phenyl-2,2'-dithioxo-2,2',3,3'-tetrahydro-1*H*,1'*H*-spiro[furo[2,3-*d*]pyrimidine-6,5'-pyrimidine]-4,4',6'(5*H*)-trione (**5ac'**), respectively (Scheme 1).

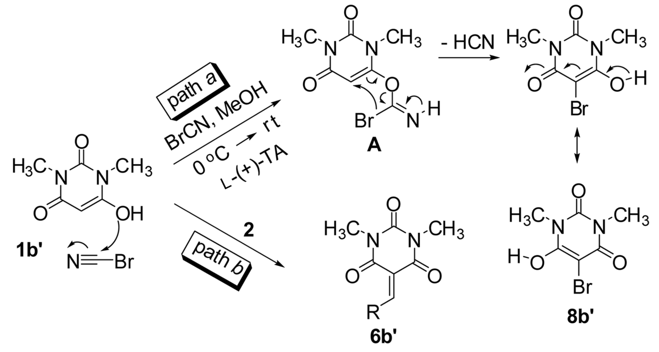
Although the mechanism of the reaction between barbituric acid and cyanogen bromide has not yet been established experimentally, a possible explanation is proposed in Scheme 2. On the basis of the well established chemistry of barbituric acid[14] and according to the mechanism of the bromination of 1-alkyl imidazoles[11] and (thio)barbituric



X-Y-X: NH-CO-NH (**a'**); MeN-CO-NMe (**b'**);NH-CS-NH (**c'**), EtN-CS-NEt (**d'**)

R: C_6H_5 (**a**); *p*-O_2N-C_6H_4 (**b**); *m*-O_2N-C_6H_4 (**c**); *o*-O_2N-C_6H_4 (**d**); *p*-NC-C_6H_4 (**e**); *p*-Br-C_6H_4 (**f**); *p*-OH-C_6H_4 (**g**); *m*-OH-C_6H_4 (**h**); *o*-OH-C_6H_4 (**i**); *o*-Cl-C_6H_4 (**j**); 2,4-di-Cl-C_6H_4 (**k**) ; 4-OH-3-CH_3O-C_6H_3 (**l**); 3-OH-4-CH_3O-C_6H_3 (**m**); 3,4,5-tri-CH_3O-C_6H_2 (**n**); *p*-CH_3O-C_6H_4 (**o**); 1-Naphthyl (**p**); 2-Furyl (**q**); 9-Anthranyl (**r**)

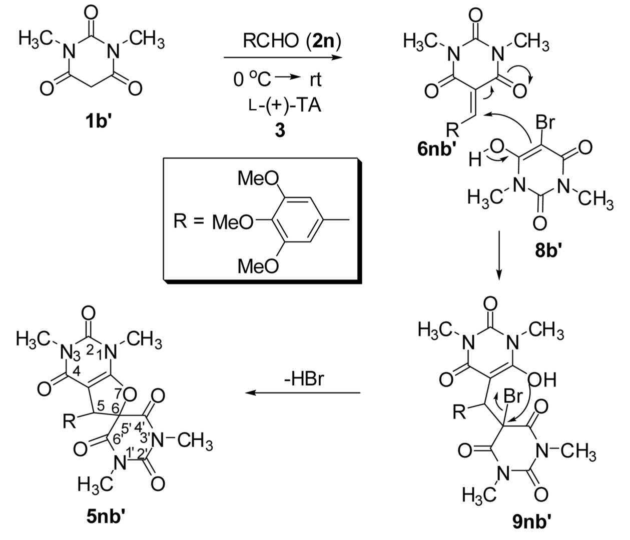
Scheme 1. Reaction of (thio)barbituric acids (**1a'-d'**) with cyanogen bromide and aldehydes in the presence of L-(+)-tartaric acid (path a) and comparison with their reaction in the presence of Et_3N (path b).



Scheme 2. Proposed mechanism for the preparation of **8b'** as a representative.

acids by cyanogen bromide under basic condition,[15,16] it is reasonable to assume that the enolic form of 1,3-dimethyl barbituric acid **1b'** (as representative) reacted with cyanogen bromide and formed an intermediate (**A**). Intramolecular rearrangement of **A** afforded 5-bromo-1,3-dimethyl barbituric acid (**8b'**) followed by loss of HCN. The compound **8b'** was also synthesized by the reaction of **1b'** with bromine.[17] Unfortunately, all attempts failed to separate or characterize **A** and **8b'** as representatives.

The proposed mechanism of the formation of **5nb'** is shown in Scheme 3 as a representative. First, the Knoevenagel condensation of **1b'**,[18] with aldehyde (**2n**) afforded 1,3-dimethyl-5-(3,4,5-trimethoxybenzylidene)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**6nb'**) then Michael addition of **8b'** to β-carbon position of **6nb'** as an α,β-unsaturated carbonyl compound gave an intermediate (**9nb'**). Unfortunately, all attempts failed to separate or characterize **9nb'**. Finally, intramolecular nucleophilic attack of oxygen anion to the carbon atom (pushing the bromide ion out) produced **5nb'** in good yield (Scheme 3). 5-Bromo-1,3-dimethylpyrimidine-(1*H*,3*H*,5*H*)-2,4,6-trione (**8b'**) was reported to react with another unsaturated carbon-carbon double bond to form 5-spirobarbiturate system under basic condition.[19,20] Recently, Elinson *et al.* has also been reported the reaction of DMBA with aldehydes in the presence of bromine under basic condition (EtONa/EtOH).[17] However, there is no report about spirocyclization reaction of **8b'** under acidic condition. The structures of the **5aa'-5qa'**, **5ab'-5qb'** and **5ac'-5qc'** were deduced from their IR, ^{1}H NMR, ^{13}C NMR spectra and mass analysis. Representatively, ^{1}H-NMR spectrum of **5nb'** (in $CDCl_3$) revealed the presence of four N-methyl protons as four distinct singlets at δ 2.67, 3.42, 3.53 and 3.79 ppm and two singlets for O-methyl protons at δ 3.32 and 3.81 ppm. The peak of C-H proton on five membered ring appeared at δ 4.84 ppm and aromatic protons as a singlet at δ 6.25 ppm integrated for 2H. The ^{13}C NMR spectrum of this compound displayed nineteen distinct peaks (see experimental section). The ^{1}H-NMR spectrum of **5qb'** (in $CDCl_3$) also revealed the presence of four N-methyl protons as four distinct singlets at δ 2.93, 3.13, 3.42 and 3.49 ppm. The peak of C-H proton on five membered ring appeared at δ 5.03 ppm and aromatic protons as a singlets at δ 6.26, 6.36 and 7.36 ppm integrated for 3H. The ^{13}C NMR spectrum of this compound also show seventeen distinct peaks (see experimental section). Furthermore, representatively, the proposed fragmentation of **5qb'** is shown in Scheme 4 and show the correct molecular ion peak at *m/z* = 388 which has 19% abundance. In these reactions, no 5-cyano barbiturates (**7a'-7d'**) were observed (Scheme 1).

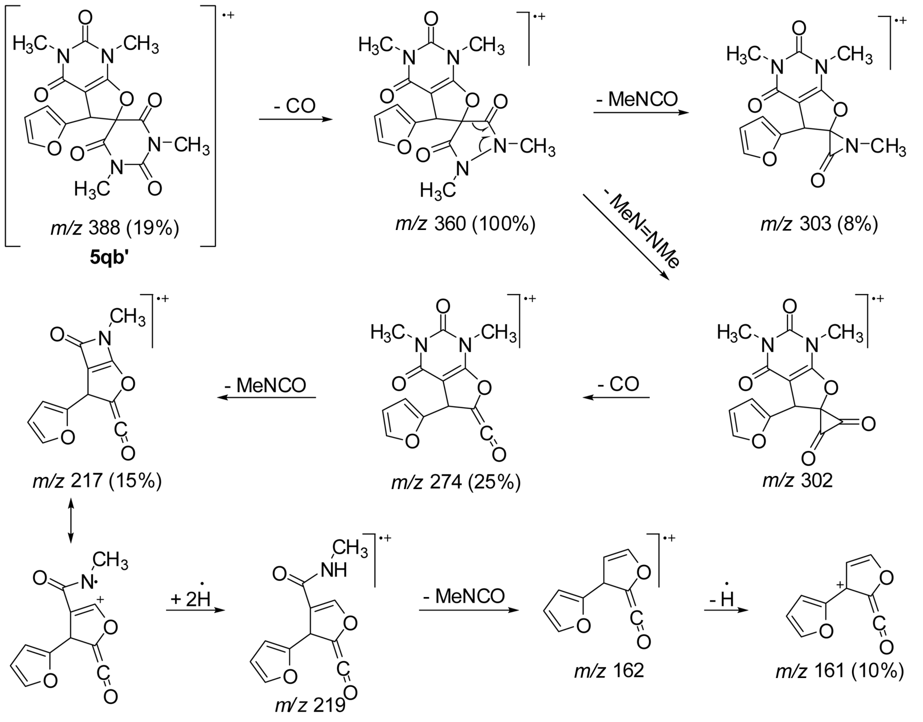


Scheme 3. Knoevenagel condensation, Michael addition and cyclization mechanism for the formation of **5nb'** as representative.

The reaction of various aldehydes (except formaldehyde) with **1a'-c'** and cyanogen bromide affords the racemic mixture of the chiral molecules of **5aa'-5qa'**, **5ab'-5qb'** and **5ac'-5qc'**. The carbon C5 is a chiral centre and is assigned with an asterisk in the formula structures of **5aa'-5qa'** through **5ac'-5qc'** (Scheme 1).

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-alkylmethylene barbituric acids in the absence of cyanogen bromide.[21-23] Barbituric acids also give mono- and bis-condensation products with aldehydes.[24,25] Therefore, according to Scheme 2, the cyanogen bromide plays the major role in formation of **8** *via* intermediate **A**. In other words, compound **8** is the key reagent for the synthesis of **5aa'-5qa'** through **5ac'-5qc'**. No **8** and **5aa'-5qa'** through **5ac'-5qc'** were observed in the absence of cyanogen bromide under the same condition! The reaction of **1d'** with cyanogen bromide and various aldehydes did not give spiro compounds **5ad'-5qd'** in the presence of L-(+)-TA under the same condition (see later).

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 (aldehydes containing strong electron-withdrawing substituents exclusively give Knoevenagel condensation then subsequently Michael adducts). The electron-withdrawing substituents on the phenyl ring in 5-arylmethylene barbituric



Scheme 4. Representatively, proposed mass fragmentation of **5qb'**.

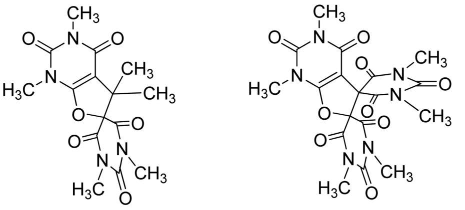
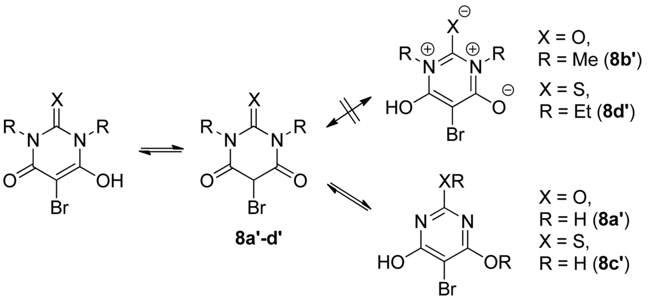


Figure 1. Structures of **10**[28] and **11**.[16]



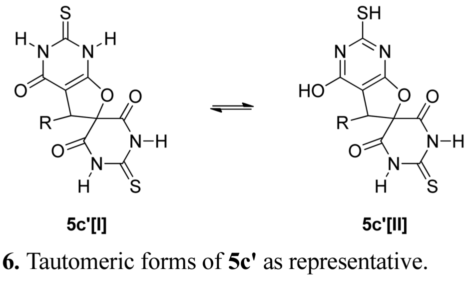
Scheme 5. Tautomeric and mesomeric forms of **8a'**-**8d'**.

acids facilitate the Michael addition of a carbanion on their β-position.[26] Owing to the aromatic nature of **8a'** and **8c'**, the nucleophile ability of these compounds is less than that of **8b'** and **8d'**. Therefore, the reactivity of these later compounds (**8b'** and **8d'**) is more than that of **8a'** and **8c'** due to amide resonance dominates over the aromaticity in barbituric acids.[27] The nucleophilicity should be decreased due to aromatic nature of pyrimidine ring moiety. With a negative charge on the barbituric acid ring, it is reasonable to assume that π-π atomic orbital overlap between atoms in the ring should increase (Scheme 5).[27]

More recently, we have investigated the reaction of barbituric acids with cyanogen bromide and ketones in the presence of triethylamine under basic condition. It has been found that the salts of **4**, dimeric (**10**,[28] as representative) and trimeric spiro barbiturate form of DMBA (**11**) were afforded in these reactions (Fig. 1).[16] In contrast, in the present research, no trimeric form **11** was observed from the reaction of DMBA **1b'** with cyanogen bromide and aldehydes under acidic condition.

The sulfur analogues of the compounds **5c'** may have two tautomeric forms. Representatively, in **5c'**, this phenomenon arose from the strong nucleophilicity of sulfur atom in thiocarbonyl group of thiouracil ring moiety, which tautomerizes to thiol functional group [thiolactim form (**5c'[II]**)] on pyrimidine ring moiety and results in the tautomeric equilibrium mixture. Therefore, the mixture of at least two distinct tautomers, thiolactam (**5c'[I]**) and thiolactim (**5c'[II]**), were existed in equilibrium mixtures of **5c'** (Scheme 6).[29,30]

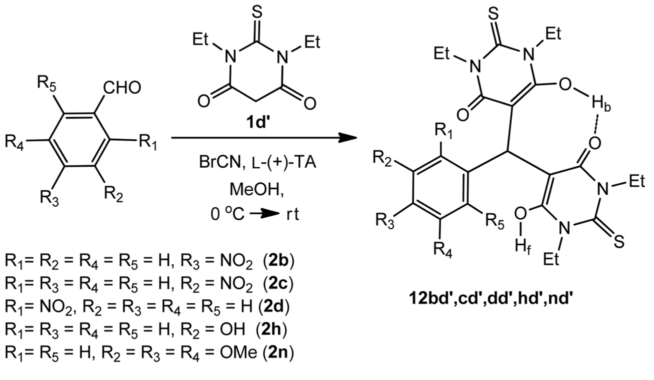
Representatively, in the reaction between **1d'** and **2c** afforded Knoevenagel condensation then subsequently Michael adducts to give 5,5'-((3-nitrophenyl)methylene)-



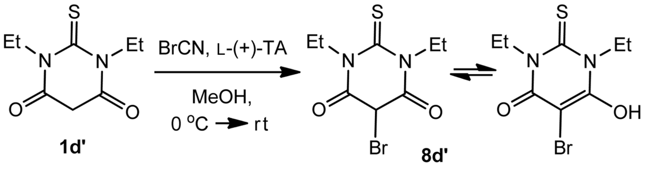
Scheme 6. Tautomeric forms of **5c'** as representative.

bis(1,3-diethyl-6-hydroxy-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one) (**12cd'**) (Scheme 7). Representatively, the structure of **12cd'** was confirmed from spectroscopic data. ^{1}H NMR spectrum of this compound (in $CDCl_3$) revealed the presence of two different chemical shifts for *N*-ethyl protons, as two distinct triplets at δ 1.302 and 1.379 ppm for methyl groups and a multiplet for two $N\text{-}CH_2$- groups at δ 4.58-4.69 ppm, respectively. A singlet for aliphatic C1-H proton at δ 5.63 ppm and two broad singlets at δ 8.43 and 14.00 ppm. A singlet at δ 6.64 (1H), a doublet at δ 6.71 (2H) and a triplet at δ 7.18 ppm (1H) at aromatic region were observed. The ^{13}C NMR spectrum of **12cd'** show fifteen distinct peaks that confirms the structure of this compound (see experimental). The reason of the formation of **12cd'** in competition with the formation of **5cd'** attributed to the strong nucleophilicity of 1,3-diethyl thiobarbituric acid **1d'**. The nucleophilicity of **1d'** stronger than that of 5-bromo-1,3-diethyl-6-hydroxy-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one (**8d'**). Therefore, **1d'** attacked to the β-carbon position of **6cd'** as Michael addition prior to formation of **8d'**. In contrast, we have detected **8d'** in the reaction of **1d'** with BrCN in the absence of aldehyde and in the presence of L-(+)-TA (Scheme 8). ^{1}H NMR spectrum of **8d'** consists of a triplet at δ 1.32 and a quartet at δ 4.57 ppm corresponds to methyl and methylene protons on ethyl groups, respectively. A singlet at δ 10.15 ppm corresponds to OH group of predominant thiolactam-enol form. ^{13}C NMR spectrum of **8d'** shows five distinct peaks at δ 175.4, 164.4, 90.3, 45.4 and 11.9 ppm that confirms the structure (see experimental). Other evidence for the formation of **8d'** (the existence of bromine atom in these molecules) was performed by Beilstein test and the wet silver nitrate test (precipitate of pale yellow silver bromide).

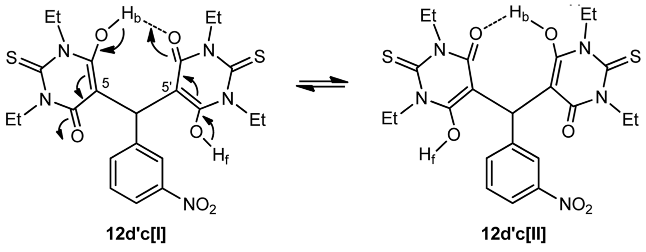
As mentioned above, the electron-withdrawing substituents on the phenyl ring in 5-arylmethylene (thio)barbituric acids (as an α,β-unsaturated carbonyl compounds) facilitate the Michael addition on their β-position.[26]



Scheme 7. Representatively, reaction of **1d'** with **2b-d**, **2h** and **2n** for the formation of **12bd'-12dd'**, **12hd'** and **12nd'** in the presence of BrCN and L-(+)-tartaric acid in methanol (H_b: H-bonding and H_f: H-free).



Scheme 8. Reaction of **1d'** with BrCN in the absence of aldehydes for the formation of **8d'**.



Scheme 9. Representatively, tautomeric forms and intramolecular H-bonding in **12cd'** (H_b: H-bonding and H_f: H-free).

Representatively, The compound **12cd'** shows an intramolecular H-bond between carbonyl group of one thiobarbituric acid ring moiety with hydroxyl group of the enolic form of another one thiobarbituric acid ring moiety (This proton assigned with H_b) (Schemes 7). The ^{1}H NMR spectrum of **12cd'** show two broad singlets at δ 8.43 and 14.00 ppm that correspond to two types of exchangeable protons (The exchangeability was examined with adding a drop of D_2O). The peak at δ 14.00 ppm corresponds to eight membered intramolecular H-bond (H_b and H_f assigned as intramolecular H-bonded and H-free, respectively in Schemes 7 and 9). This phenomenon was observed for aldehydes including electron donor and withdrawing substituents in the reaction with **1d'** in the presence of BrCN and L-(+)-TA. Any of these type barbiturates having amidic (-CO-NH-) and/or thioamidic protons (-CS-NH-) do not show eight membered intramolecular H-bond. It seems that this phenomenon was arisen from tautomerization of (thio)barbituric acids (lactam-thiolactam ⇄ lactim-thiolactim forms) that occurred prior to formation of intramolecular H-bond. Therefore, among of these compounds, *N,N*-dialkylated thiobarbituric acid **1d'**, only show eight membered intramolecular H-bond. Other compounds consist of eight membered intramolecular H-bond have also been reported.[31-36] The compound 9-anthranaldehyde (**2r**) exclusively gave Knoevenagel adducts (**6ra'-6rd'**) in the reaction with BrCN and **1a'-1d'** in the presence of L-(+)-TA under the same condition (Scheme 1).

Conclusion

In summary, the reaction of BA, DMBA, TBA and DETBA with cyanogen bromide and aldehydes in the presence of L-(+)-tartaric acid was used to develop an efficient synthetic procedure to prepare dimeric stable spiro (thio)barbiturates; 5-aryl-1*H*,1'*H*-spiro[furo[2,3-*d*]pyrimidine-6,5'-pyrimidine]-2,2',4,4',6'(3*H*,3'*H*,5*H*)-pentaones and their sulfur analogues. We also concluded that DMBA and DETBA are more reactive than that of BA and TBA in details. The experimental results indicated that the aromatic aldehydes are more reactive than that of aliphatics. The aromatic aldehydes possessing electron-withdrawing substituent are more reactive than that of electron-donating substituent. In the reaction with DETBA, the aromatic aldehydes possessing electron donor and electron-withdrawing substituents were afforded Knoevenagel condensation then subsequently Michael adducts. All the obtained spiro compounds were the racemic mixtures.

Experimental Section

General Procedures. The drawing and nomenclature of compounds is proceeded by ChemBioDraw Ultra 12.0 version software. Melting points were measured with an Electrothermal digital apparatus and were uncorrected. IR spectra were determined 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. 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). 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 compounds **1c'** was synthesized and purified in our laboratory as described in the literature previously.[37] Cyanogen bromide was synthesized based on reported references.[38] Compounds **1a'**, **1b'**, **1d'**, L-(+)-tartaric acid and used solvents purchased from Merck without further purification.

General procedures for the preparation of **5aa'-5aq'** through **5ac'-5qc'**, **8d'**, **12bd'-dd'**, **12hd'** and **12nd'**.

The physical and spectral data of the selected compounds from **5aa'-5aq'** through **5ac'-5qc'**, **8d'**, **12bd'-dd'**, **12hd'** and **12nd'** are follows as representatives.

In a 10 mL with Teflon-faced screw cap tube equipped by a magnetically stirrer, dissolved 0.15 g (0.96 mmol) 1,3-dimethyl barbituric acid, 0.015 g (0.48 mmol) benzaldehyde and 0.8 g L-(+)-tartaric acid in 10 mL methanol and then 0.06 g (0.48 mmol) cyanogen bromide (BrCN) was added into solution at 0 °C. The reaction mixture was stirred for 2 h at 0 °C to room temperature. 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). The crystalline white solid precipitate, filtered off, washed with few mL methanol and dried. (0.12 g, 70% yield).

1,1',3,3'-Tetramethyl-5-phenyl-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 (5ab'). White solid (50%); mp = 206-208 °C (decomps.); FT-IR (KBr) 3427, 3005, 3010, 2961, 1698 (C=O), 1675 (C=O), 1650 (C=O), 1516 (C=C ar.), 1432 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.57 (s, 3H, NCH_3), 3.31 (s, 3H, NCH_3), 3.44 (s, 3H, NCH_3), 3.53 (s, 3H, NCH_3), 4.93 (s, 1H, CH aliph.), 7.06-7.53 (m, 5H, ar.); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.5, 163.0, 162.7, 158.6, 151.2, 149.6, 132.8, 129.5, 128.9, 128.2, 90.2, 85.5, 59.3, 30.0, 29.5, 28.4, 28.2.

5-(4-Bromophenyl)-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 (5fa'). White solid (55%); mp = 289-290 °C (decomps.); FT-IR (KBr) 3422, 3251, 3070, 2925, 2853, 1719 (C=O), 1659 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.81 (s, 1H, CH aliph.), 7.10 (d, 2H, J = 8.4 Hz, CH ar.), 7.48 (d, 2H, J = 8.4 Hz, CH ar.), 10.87 (s, 1H, NH), 11.10 (s, 1H, NH), 11.61 (s, 1H, NH), 12.69 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 167.2, 164.9, 164.2, 160.2, 151.2, 149.7, 134.8, 131.6, 131.5, 122.3, 89.4, 86.0, 62.5.

5-(4-Bromophenyl)-1,1',3,3'-tetramethyl-1*H*,1'*H*-spiro[furo[2,3-*d*]pyrimidine-6,5'-pyrimidine]-2,2',4,4',6'(3*H*,3'*H*,5H)-pentaone (5fb'). White solid (65%); mp = 267-269 °C; FT-IR (KBr) 3100, 2957, 1697 (C=O), 1677 (C=O), 1656 (C=O), 1515 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.68 (s, 3H, NCH_3), 3.31 (s, 3H, NCH_3), 3.45 (s, 3H, NCH_3), 3.35 (s, 3H, NCH_3), 4.88 (s, 1H, CH aliph.), 6.96 (d, 2H, J = 8.4 Hz, CH ar.), 7.48 (d, 2H, J = 8.4 Hz, CH ar.); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.3, 162.8, 158.5, 151.1, 149.5, 145.0, 132.1, 131.9, 129.9, 123.7, 89.8, 85.2, 58.5, 30.0, 29.6, 28.5, 28.2.

5-(2-Chlorophenyl)-1,1',3,3'-tetramethyl-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 (5jb'). White solid (55%); mp = 282-284 °C (decomps.); FT-IR (KBr) 3050, 2956, 1700 (C=O), 1677 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.71 (s, 3H, NCH_3), 3.28 (s, 3H, NCH_3), 3.40 (s, 3H, NCH_3), 3.52 (s, 3H, NCH_3), 5.58 (s, 1H, CH aliph.), 7.17 (dd, 1H, ^3J = 5.7 Hz, ^4J = 3.6 Hz, CH ar.), 7.29 (m, 2H, CH ar.), 7.38 (m, 1H, CH ar.); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.2, 163.1, 162.8, 158.4, 151.2, 149.5, 133.8, 130.9, 130.7, 130.5, 129.5, 127.4, 88.7, 85.5, 54.3, 30.0, 29.4, 28.4, 28.2; MS, m/z 434 (M^++2, 2%), 432 (M^+, 5%), 397 (95), 367 (3), 340 (15), 317 (3), 283 (100), 268 (2), 255 (5), 239 (3), 226 (14), 211 (3), 198 (4), 176 (20), 163 (9), 149 (5), 136 (25), 113 (8), 99 (6), 75 (6), 58 (20), 42 (4).

5-(2-Chlorophenyl)-2,2'-dithioxo-2,2',3,3'-tetrahydro-1*H*,1'*H*-spiro[furo[2,3-*d*]pyrimidine-6,5'-pyrimidine]-4,4',6'(5*H*)-trione (5jc'). Yellow solid (60%); mp = 206-208 °C (decomps.); FT-IR (KBr) 3425, 3001, 2922, 1627, 1531, 1439, 538 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 5.89 (bs, 1H, CH aliph.), 7.17-7.84 (m, 4H, CH ar.), 10.88 (bs, 1H, NH), 11.34 (bs, 1H, NH), 11.47 (bs, 1H, NH), 12.08 (bs, 1H, NH); MS, m/z 410 (M^++2, 0.3%), 408 (M^+, 1%), 292 (1), 231 (100), 215 (7), 172 (80), 144 (35), 128 (8), 116 (18), 101 (24), 86 (60), 69 (15), 58 (18).

5-(2,4-Dichlorophenyl)-1,1',3,3'-tetramethyl-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 (5kb'). White solid (80%); mp = 268-270 °C (decomps.); FT-IR (KBr) 3100, 2925, 1699 (C=O), 1674 (C=O), 1519 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.80, (s, 3H, NCH_3), 3.32 (s, 3H, NCH_3), 3.40 (s, 3H, NCH_3), 3.51 (s, 3H, NCH_3), 5.49 (s, 1H, CH aliph.), 7.11 (d, 1H, J = 8.7 Hz, CH ar.), 7.27 (dd, 2H, ^3J = 8.7 Hz, ^4J

= 2.1 Hz, CH ar.), 7.41 (d, 1H, ^4J = 2.1 Hz, CH ar.); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 165.1, 163.0, 162.8, 158.3, 151.1, 149.4, 135.9, 134.3, 131.8, 129.4, 129.3, 127.9, 88.3, 85.3, 53.8, 30.0, 29.4, 28.5, 28.2.

5-(4-Hydroxy-3-methoxyphenyl)-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 (5la'). White solid (50%); mp = 243-245 °C; FT-IR (KBr) 3436, 3214, 2926, 2850, 1721 (C=O), 1666 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.65 (s, 3H, OCH$_3$), 4.66 (s, 1H, CH aliph.), 6.47 (d, 2H, J = 8.1 Hz, CH ar.), 6.63 (d, 2H, J = 7.8 Hz, CH ar.), 9.05 (s, 1H, OH), 10.80 (s, 1H, NH), 11.05 (s, 1H, NH), 11.56 (s, 1H, NH), 12.60 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 167.5, 164.6, 164.5, 160.3, 151.2, 149.9, 147.5, 147.2, 125.4, 121.7, 115.5, 113.3, 90.0, 86.0, 56.4, 55.9.

5-(4-Hydroxy-3-methoxyphenyl)-1,1',3,3'-tetramethyl-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 (5lb'). White solid (60%); mp = 260-262 °C; FT-IR (KBr) 3411, 3100, 2961, 2926, 2854, 1713 (C=O), 1685 (C=O), 1652 (C=O), 1520 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 2.66 (s, 3H, NCH$_3$), 3.33 (s, 3H, NCH$_3$), 3.43 (s, 3H, NCH$_3$), 3.54 (s, 3H, NCH$_3$), 3.82 (s, 3H, OCH$_3$), 4.87 (s, 1H, CH aliph.), 5.98 (bs, 1H, OH), 6.49 (d, 1H, ^4J = 1.8 Hz, CH ar.), 6.55 (dd, 1H, ^3J = 8.1 Hz, ^4J = 1.8 Hz, CH ar.), 6.79 (d, 1H, J = 8.1 Hz, CH ar.); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 165.5, 163.2, 162.6, 158.6, 151.2, 149.7, 146.9, 146.7, 124.2, 121.5, 114.8, 110.4, 91.0, 85.6, 59.4, 56.0, 30.0, 29.5, 28.6, 28.2.

5-(3,4,5-Trimethoxyphenyl)-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 (5na'). White solid (55%); mp = 267-269 °C; FT-IR (KBr) 3446, 3032, 2846, 1731 (C=O), 1671 (C=O), 1653, 1375, 1127 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.64 (s, 3H, OCH$_3$), 3.67 (s, 6H, 2OCH$_3$), 4.75 (s, 1H, CH aliph.), 6.42 (s, 2H, CH ar.), 10.83 (s, 1H, NH), 11.10 (s, 1H, NH), 11.60 (s, 1H, NH), 12.63 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 167.3, 164.9, 164.5, 160.3, 152.9, 151.2, 150.0, 138.0, 130.4, 106.8, 89.8, 85.7, 60.4, 56.5, 56.3; MS, *m/z* 432 (M$^+$, 1%), 428 (2), 368 (3), 343 (85), 314 (6), 287 (10), 233 (15), 196 (14), 153 (100), 127 (50), 92 (25), 77 (15), 57 (10), 43 (12).

1,1',3,3'-Tetramethyl-5-(3,4,5-trimethoxyphenyl)-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 (5nb'). White solid (60%); mp = 205-207 °C; FT-IR (KBr) 3425, 3050, 2926, 2848, 1712 (C=O), 1687 (C=O), 1666 (C=O), 1382 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 2.67 (s, 3H, NCH$_3$), 3.32 (s, 6H, 2OCH$_3$), 3.42 (s, 3H, NCH$_3$), 3.53 (s, 3H, NCH$_3$), 3.79 (s, 3H, NCH$_3$), 3.81 (s, 3H, OCH$_3$), 4.84 (s, 1H, CH aliph.), 6.25 (s, 2H, CH ar.); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 165.4, 163.1, 162.7, 158.6, 153.5, 151.2, 149.7, 138.9, 128.1, 105.3, 90.4, 85.3, 60.8, 59.8, 56.2, 30.0, 29.4, 28.7, 28.2; MS, *m/z* 488 (M$^+$, 60%), 457 (10), 441 (6), 416 (12), 359 (12), 333 (100), 305 (18), 276 (10), 248 (10), 232 (5), 219 (6), 200 (10), 187 (8), 168 (6), 116 (7), 101 (6), 69 (5), 58 (12).

5-(4-Methoxyphenyl)-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 (5oa'). White solid (55%); mp = 280-282 °C; FT-IR (KBr) 3421, 3257, 2923, 2853, 1730 (C=O), 1719 (C=O), 1656, 1369, 1248 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.71 (s, 3H, OCH$_3$), 4.71 (s, 1H, CH aliph.), 6.82 (d, 2H, J = 8.4 Hz, CH ar.), 7.03 (d, 2H, J = 8.4 Hz, CH ar.), 10.82 (s, 1H, NH), 11.04 (s, 1H, NH), 11.58 (s, 1H, NH), 12.63, (bs, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 167.5, 164.6, 164.4, 160.3, 159.7, 151.2, 149.8, 130.4, 127.0, 113.9, 89.8, 86.3, 55.6, 55.5.

5-(4-Methoxyphenyl)-1,1',3,3'-tetramethyl-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 (5ob'). White solid (60%); mp = 218-220 °C; FT-IR (KBr) 3010, 2926, 2851, 1716 (C=O), 1692 (C=O), 1674 (C=O), 1515 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 2.65 (s, 3H, NCH$_3$), 3.31 (s, 3H, NCH$_3$), 3.43 (s, 3H, NCH$_3$), 3.53 (s, 3H, NCH$_3$), 3.78 (s, 3H, OCH$_3$), 4.89 (s, 1H, CH aliph.), 6.85 (d, 2H, J = 8.7 Hz, CH ar.), 6.99 (d, 2H, J = 8.7 Hz, CH ar.); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 165.5, 163.1, 162.5, 160.4, 158.6, 151.2, 149.6, 129.4, 124.6, 114.3, 90.3, 85.7, 58.8, 55.3, 29.9, 29.5, 28.5, 28.2.

1,1',3,3'-Tetramethyl-5-(naphthalen-1-yl)-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 (5pb'). Yellow solid (65%); mp = 257-259 °C; FT-IR (KBr) 3059, 2955, 1698 (C=O), 1671 (C=O), 1518 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 2.14 (s, 3H, NCH$_3$), 3.33 (s, 3H, NCH$_3$), 3.35 (s, 3H, NCH$_3$), 3.54 (s, 3H, NCH$_3$), 5.98 (s, 1H, CH aliph.), 7.34 (d, 1H, J = 7.2 Hz, CH ar.), 7.44-7.53 (m, 3H, CH ar.), 7.65-7.68 (m, 1H, CH ar.), 7.83-7.91 (m, 2H, CH ar.); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 165.6, 163.2, 162.9, 158.6, 151.3, 148.8, 133.7, 131.2, 129.7, 129.6, 127.6, 127.5, 126.2, 126.0, 125.5, 120.9, 89.8, 85.6, 53.9, 30.0, 29.3, 28.3, 28.0; MS, *m/z* 448 (M$^+$, 100%), 430 (7), 345 (5), 332 (35), 306 (25), 293 (70), 275 (10), 249 (15), 236 (45), 220 (10), 207 (8), 192 (30), 179 (28), 165 (18), 152 (25), 127 (10), 96 (5), 58 (12).

5-(2-Furyl)-1,1',3,3'-tetramethyl-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 (5qb'). White solid (70%); mp = 236-238 °C; FT-IR (KBr) 3100, 2960, 2925, 1715 (C=O), 1696 (C=O), 1515, 1038 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 2.93 (s, 3H, NCH$_3$), 3.31 (s, 3H, NCH$_3$), 3.42 (s, 3H, NCH$_3$), 3.49 (s, 3H, NCH$_3$), 5.03 (s, 1H, CH aliph.), 6.26 (s, 1H, CH ar.), 6.36 (s, 1H, CH ar.), 7.36 (s, 1H, CH ar.); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 165.1, 162.7, 162.6, 158.5, 151.0, 149.7, 146.7, 143.6, 111.4, 111.0, 88.7, 83.6, 52.1, 29.9, 29.6, 29.1, 28.2; MS, *m/z* 388 (M$^+$, 19%), 360 (100), 343 (18), 318 (5), 303 (8), 288 (10), 274 (25), 260 (5), 246 (25), 232 (24), 217 (15), 175 (8), 161 (10), 146 (5), 132 (25), 106 (7), 92 (30), 66 (17), 42 (4).

5-Bromo-1,3-diethyl-6-hydroxy-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one (8d'). White solid; mp = 224 °C; FT-IR (KBr) 3435 (OH), 2981, 2933, 1633 (C=O), 1379, 1259, 1109 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.32 (t, 6H, J = 6.9 Hz), 4.57 (q, 4H, J = 6.9 Hz), 10.15 (s, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 175.4, 164.4, 90.3, 45.4, 11.9.

5,5'-((3-Nitrophenyl)methylene)bis(1,3-diethyl-6-hydroxy-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one) (12cd').

White solid (70%); mp = 206-207 °C; FT-IR (KBr) 3435, 3030, 2982, 2932, 1620, 1528, 1434, 1380, 1266, 1109 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.30 (t, 6H, J = 6.9 Hz), 1.38 (t, 6H, J = 6.9 Hz), 4.58-4.70 (m, 8H), 5.63 (s, 1H), 6.64 (s, 1H), 6.70 (d, 2H, J = 4.8 Hz), 7.20 (t, 1H, J = 7.8 Hz), 8.43 (bs, 1H), 14.00 (bs, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 174.5, 163.7, 162.2, 155.8, 137.7, 129.6, 118.7, 113.7, 113.6, 97.3, 45.1, 44.6, 34.8, 12.1, 12.0.

5,5'-((2-Nitrophenyl)methylene)bis(1,3-diethyl-6-hydroxy-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one) (12dd'). White solid (70%); mp = 212-214 °C; FT-IR (KBr) 3438, 3050, 2981, 2934, 1691, 1620, 1528, 1487, 1380, 1264, 1110 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.27-1.40 (m, 12H), 4.52-4.68 (m, 8H), 6.11 (s, 1H), 7.28 (d, 1H, J = 7.5 Hz), 7.42 (t, 1H, J = 7.5 Hz), 7.51-7.60 (m, 2H), 9.72, (bs, 1H), 14.00 (bs, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 174.4, 164.4, 163.6, 162.0, 150.1, 132.7, 131.3, 129.5, 128.0, 124.1, 96.6, 45.4, 45.1, 32.6, 11.9.

5,5'-((3-Hydroxyphenyl)methylene)bis(1,3-diethyl-6-hydroxy-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one) (12hd'). White solid (70%); mp = 244 °C; FT-IR (KBr) 3458, 2982, 2932, 1620, 1432, 1377, 1265, 1109 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.30 (t, 6H, J = 6.9 Hz), 1.38 (t, 6H, J = 6.9 Hz), 4.58-4.70 (m, 8H), 5.63 (s, 1H), 6.64 (s, 1H), 6.71 (d, 2H, J = 7.5 Hz), 7.19 (t, 1H, J = 7.8 Hz), 8.06 (bs, 2H), 14.00 (bs, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 174.6, 163.7, 162.2, 155.8, 137.7, 129.6, 118.8, 113.7, 113.5, 97.3, 45.1, 44.6, 34.8, 12.1, 12.0.

5,5'-((3,4,5-Trimethoxyphenyl)methylene)bis(1,3-diethyl-6-hydroxy-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one) (12nd'). White solid (70%); mp = 155 °C; FT-IR (KBr) 3436, 2977, 2934, 2525, 1619, 1427, 1381, 1267, 1108 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.30 (t, 6H, J = 6.9 Hz), 1.37 (t, 6H, J = 6.9 Hz), 3.76 (s, 6H), 3.84 (s, 3H), 4.50-4.70 (m, 8H), 5.62 (s, 1H), 6.31 (s, 2H), 12.10 (bs, 1H), 13.9 (bs, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 174.6, 163.7, 162.2, 153.2, 137.1, 131.1, 104.1, 97.5, 60.9, 56.4, 45.2, 44.5, 34.9, 12.1, 12.0.

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Supplementary Material. Full characterization data of compounds **5aa'-5aq'** through **5ac'-5qc'**, **8d'**, **12bd'-dd'**, **12hd'** and **12nd'** are available.

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