One-pot Reaction of Mono and Dialdehydes with Unsymmetrical 1-methyl Barbituric Acid (1-MBA) and BrCN in the Presence of Triethylamine and L-(+)-tartaric Acid

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Abstract- **One-pot reaction of unsymmetrical 1-methybarbituric acid (1-MBA), BrCN, mono- and dialdehydes in the presence of L-(+)-tartaric acid (L-(+)-TA) and/or triethylamine afforded diastereomeric mixtures of a series of stable heterocyclic mono- and bis-spiro barbiturates and their sulfur analogues which are dimeric forms of barbiturate (uracil and thiouracil derivative) at the range of 0°C to room temperature. The reaction of symmetrical (thio)barbituric acids with dialdehydes were afforded bis-spiro barbiturates instead, 1-MBA was afforded diastereomeric mixture of bis-spiro barbiturates under the same condition. Diastereoselectively reaction products in the presence of L-(+)-TA were also investigated. Structure elucidation is carried out by ^{1}H NMR, ^{13}C NMR, FT-IR and Mass analyses. Mechanism of the formation is discussed.**

Keywords- Diastereoselective; Unsymmetrical Barbituric Acid; Spiro[furo[2;3-d] Pyrimidine; BrCN; Uracil; Thiouracil; L-(+)-tartaric Acid

I. INTRODUCTION

Many of the heterocyclic furo [2, 3-*d*] pyrimidines [1], spirobarbituric acids [2] and fused uracils [3, 4] are well known of their wide varieties of pharmaceutical and biological effects.

Barbituric acid reacted with BrCN in the presence of pyridine derivatives as König reaction. In this reaction, the pyridine derivative reacts with BrCN 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 BrCN have been used.

Chiral tartaric acid (TA) and its derivatives have been used in several asymmetric synthesis such as Sharpless asymmetric epoxidation [8-10], asymmetric hydrogenation [11], as a suitable auxiliary in the Simmons-Smith cyclopropanation reaction [12-15], enantioselective oxidation of sulfides to chiral sulfoxides in the presence of titanium tetraisopropoxide [Ti(OiPr)4] [16-18], resolution of (±)-α-methylbenzylamine as resolving agent [19], enantioselective hydrogenation of methyl 4-(4-biphenylyl)-3-oxobutanoate over a tartaric acid-modified Raney nickel catalyst [20], enantioselective Diels–Alder reaction of o-quinodimethanes by utilizing tartaric acid ester as a chiral auxiliary [21], asymmetric dialkynylation reaction of α-dinitrone by utilizing tartaric acid ester as a chiral auxiliary [22] enantioseparation of amino acids [23], resolution of *N*-methylamphetamine enantiomers with tartaric acid derivatives by supercritical fluid extraction [24], resolution of racemic *trans*-1,2-cyclohexanediol with tartaric acid [25], resolution of racemic *trans*-2-benzylaminocyclohexanol with di-*p*-toluoyl-L-tartaric acid [26], and etc.

BrCN is a very useful reagent for the synthesis of cyanamides [27] cyanates [28], and also is utilized in a selective cleavage of the methionyl peptide bonds in ribonuclease [29], and etc. BrCN also is a useful brominating agent such as; the bromination and cyanation of imidazoles [30], free radical reaction with alkanes (bromination of alkanes) [31] and α-bromination of β-aminoenones [32].

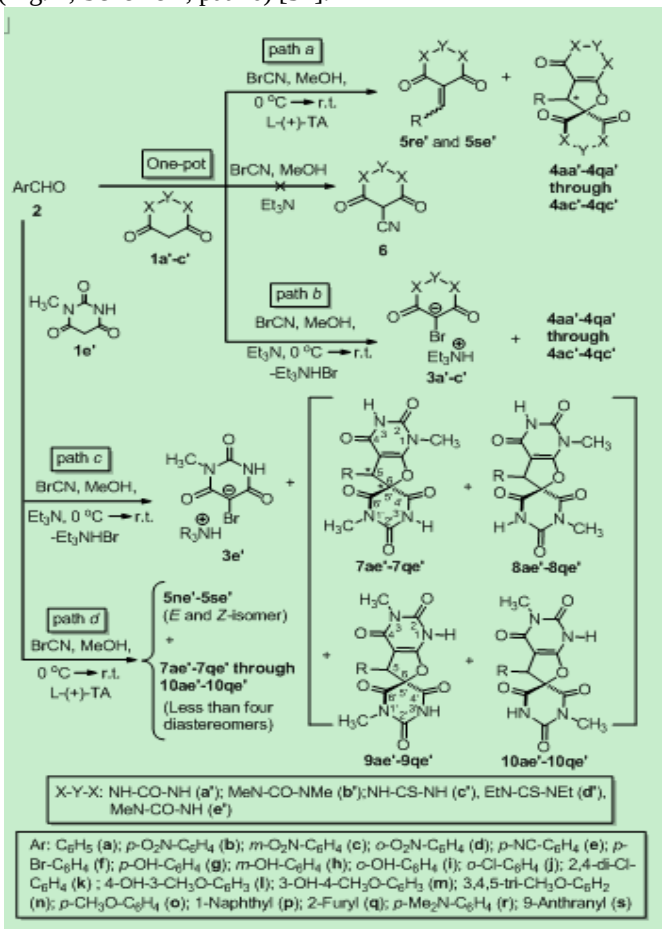
Recently, we have reported the synthesis of 5-aryl-1*H*,1'*H*-spiro[furo[2,3-*d*]pyrimidine-6,5'-pyrimidine]2,2',4,4',6'(3*H*,3'*H*,5*H*)-pentaones and their sulfur analogues derived from the reaction of symmetrical (thio)barbituric acids with aliphatic and aromatic aldehydes [33] and ketones [34,35] in the presence of BrCN and triethylamine and also in the reaction with aromatic aldehydes and BrCN in the presence of L-(+)-TA [36]. More recently, we also have reported the reaction of 1-methyl barbituric acid as an unsymmetrical barbituric acid with aromatic monoaldehydes and BrCN in the presence of triethylamine and/or pyridine [37]. Based on these concepts, in continuation, herein we report the one-pot reaction of aromatic mono- and dialdehydes with unsymmetrical 1-MBA with BrCN in the presence of L-(+)-TA and comparison with the diastereomeric products derived in the presence of triethylamine.

II. RESULTS AND DISCUSSION

This article describes the one-pot reaction of 1-MBA, BrCN and aromatic mono- and dialdehydes in the presence of L-(+)-TA to afford diastereoselectively a class of stable heterocyclic mono- and bis-spiro barbiturate compounds and comparison of its reaction products in both acidic (L-(+)-TA) and basic (triethylamine) conditions. Representatively, we have reported the reaction of barbituric (BA, **1a'**), 1,3-dimethyl barbituric acid (DMBA, **1b'**) and thiobarbituric acid TBA (**1c'**) with BrCN and benzaldehyde (**2a**) in the presence of L-(+)-TA in methanol that afforded a series 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 (**4aa'**), 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 (**4ab'**) 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 (**4ac'**), respectively in good yields (Scheme 1, path *a*) [36].

However, these spiro compounds and the salts of **3a'-3c'** were also obtained in the presence of triethylamine (Scheme 1, path *b*) [33].

Representatively, the one-pot reaction of 1-MBA (**1e'**), BrCN and benzaldehyde (**2a**) in the presence of triethylamine in methanol afforded diastereomeric mixtures of maximum four class of heterocyclic stable compounds (5*S*,5'*S*)-1,1'-dimethyl- (**7ae'**), (5*S*,5'*R*)-1,1'-dimethyl- (**8ae'**), (5*S*,5'*S*)-1',3-dimethyl- (**9ae'**) and (5*S*,5'*R*)-1',3-dimethyl-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 (**10ae'**) in good yield, respectively (and also their corresponding four enantiomers) (Fig. 1, Scheme 1, path *c*) [37].



Scheme 1 Reaction of aromatic mono aldehydes **2** with symmetrical (thio)barbituric acids (**1a'-d'**) and BrCN in the presence of L-(+)-TA (path *a*) [36], triethylamine (path *b*) [33]. The reaction of **2** with 1-MBA (**1e'**) and BrCN in the presence of triethylamine (path *c*) [37] and L-(+)-TA (path *d*)

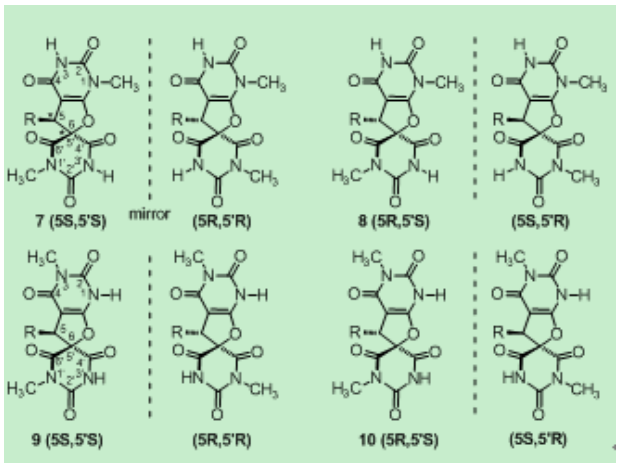
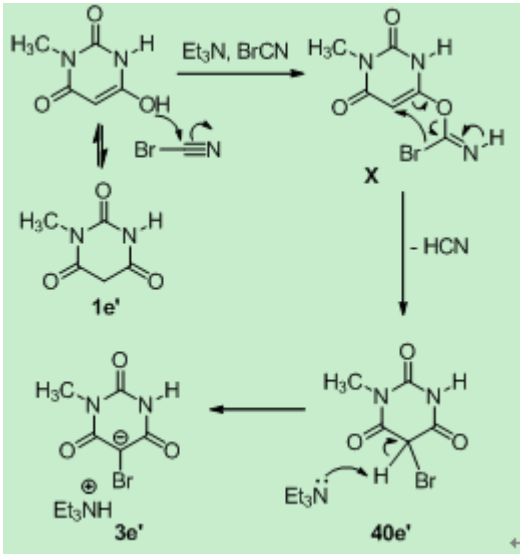


Fig. 1 Possible four diastereomers (eight stereoisomers) of **7-10** derived from reaction between **1e'** and **2** in the presence of BrCN and triethylamine and/or pyridine

The reaction of **1e'** with BrCN and **2** was also afforded the salt of triethylammonium-5-bromo-2, 4, 6-trioxohexahydro-1-methylpyrimidin-5-ide (**3e'**) in the presence of triethylamine in methanol.

In continuation of these researches, we have performed and report the diastereoselectively one-pot reaction of 1-MBA **1e'** as an unsymmetrical barbituric acid with BrCN and aromatic monoaldehydes in the presence of L-(+)-TA (Scheme 1, path d). In this research, the reaction of **1e'** with aromatic dialdehydes such as phthalaldehyde (**11a''**), isophthalaldehyde (**11b''**) and terphthalaldehyde (**11c''**) in the presence of BrCN and triethylamine and L-(+)-TA was also performed (see later).

We have reported that the salts of **3a'-3c'** and **3e'** plays a major role for the synthesis of **4** and **7-10** in the reaction with symmetrical **1a'-1c'** and unsymmetrical barbituric acid **1e'**, respectively (Scheme 1, paths *b* and *c*) [33, 37]. The mechanism for the formation of **3e'** is shown in Scheme 2 [37].



Scheme 2 Proposed mechanism for the preparation of **3e'**

The enol form of **1e'** reacts directly with BrCN to form intermediate **X**. Intramolecular rearrangement of this intermediate produces 5-bromo-1-methylpyrimidine-2, 4, 6(1*H*, 3*H*, 5*H*)-trione (5-bromo-1-MBA **40e'**) followed by loss of HCN to form the salt of triethylammonium-5-bromo-2, 4, 6-trioxohexahydro-1-methylpyrimidin-5-ide **3e'**. The salt of triethylammonium hydrobromide was also observed. Unfortunately, all attempts failed to separate or characterize **X**, **40e'** and **3e'**. In contrast, we trapped, isolated and characterized the structures of pyridinium 1-methyl-2, 4, 6-trioxohexahydropyrimidin-5-ide (**41e'**) (Fig. 2) [37] and **3a'-3c'** salts [33].

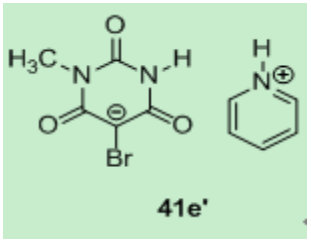


Fig. 2 Formula structure of pyridinium 1-methyl-2, 4, 6-trioxohexahydropyrimidin-5-ide **41e'** [37]

There are maximum eight possible spiro stereoisomers (four or less than four diastereomers) were synthesized from the reaction of **1e'** with **2a-q** in the presence of BrCN and triethylamine (Fig. 1). Representatively, the reaction of **1e'** with **2n** was obtained at least four diastereomers (Fig. 3a). Instead, in this reaction (reaction of **1e'** with **2n**) in the presence of BrCN and L-(+)-TA was afforded only two diastereomers under the same condition (Fig. 3b).

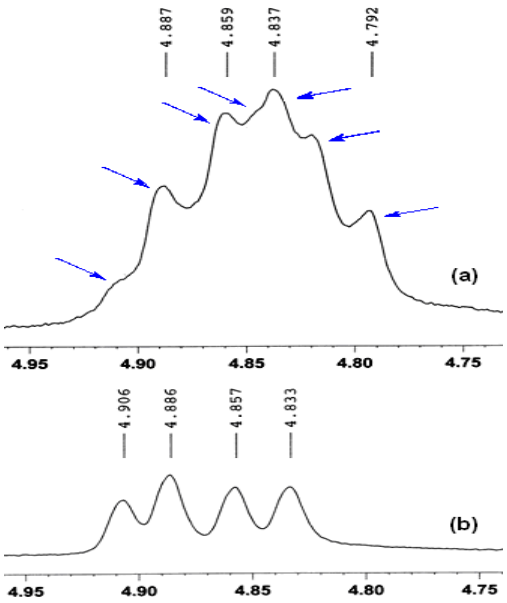
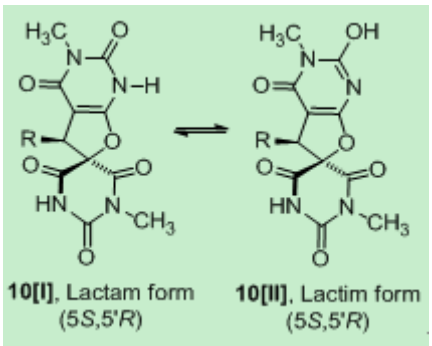


Fig. 3 Expanded C5-H proton's peaks of an equilibrium mixture of lactam and lactim forms of diastereomeric mixture of **7ne', 8ne', 9ne'** and **10ne'** derived from the one-pot reaction of **1e'** with **2n** in the presence of BrCN and triethylamine (a) and diastereoselective formation of **7ne'** and **8ne'** (and/or **9ne'** and **10ne'**) in the presence of L-(+)-TA (b) (The NMR solvent was DMSO-d_6)

These observations indicated that L-(+)-TA as a chiral auxiliary controlled the reaction stereoselectivity (see later). The existence of seven overlapped singlets for C5-H proton of diastereomeric mixture of **7ne'-10ne'** revealed that there is presumably an equilibrium mixture of lactam and lactim forms (each diastereomer consists of an equilibrium mixture of lactam and lactim forms). Instead, in the presence of L-(+)-TA, two diastereomers only were obtained and indicated that each diastereomer has both lactam and lactim forms (Scheme 3).



Scheme 3 Representatively, an equilibrium mixture of lactam (**10[I]**) and lactim forms **10[II]**) of **10** (see Scheme 1)

For instance, ^{1}H and ^{13}C NMR spectrum of the reaction between **1e'** and **2c** shows exclusively one product of among **7ce'-10ce'**. ^{1}H NMR spectrum of product shows a singlet for C5-H at δ 5.26 ppm. ^{13}C NMR spectrum shows fifteen distinct peaks (two distinct peaks for N-CH_3 carbon atoms). These data shows the diastereoselectivity of the reaction in the presence of L-(+)-TA. In contrast, **2c** gives four mixtures of diastereomers (**7ce'-10ce'**) in the presence of triethylamine and/or pyridine [37]. Four possible diastereomers were also obtained in the reaction of **1a'** and **2n** (as a representative) in the presence of BrCN and triehylamine (basic condition) [37].

Another evidence for the diastereoselective formation of **7-10** in the reaction of **1e'** with **2** and BrCN in the presence of L-(+)-TA is shown in Fig. 4. For instance, there are four different chemical shifts for N-CH_3 in **4nb'** (derived from the reaction between **1b'** and **2n**) (Fig. 4a) while there are two different chemical shift environments for N-CH_3 of spiro compound derived from the reaction between **1e'** and **2n** in the presence of L-(+)-TA (Fig. 4b). These observations indicate the diastereoselective formation two diastereomers among of **7ne'-10ne'**. Number of diastereomers derived from some mono- and dialdehydes in the reaction with **1e'** and BrCN in the presence of L-(+)-TA and the percent of each diastereomer was summarized in Table Ⅰ.

TABLE Ⅰ NUMBER OF DIASTEREOMER(S) WERE OBTAINED IN THE REACTION OF **1e'** WITH ALDEHYDES AND BRCN IN THE PRESENCE OF L-(+)-TA

Entry	Aldehyde	Number of diastereomer(s)	Percent of each diastereomer (%)
1	2c	1	100
2	2e	2	36.9, 63.1
3	2f	3	55.8, 38.9, 5.3
4	2m	1	100
5	2n	2	50, 50
6	11a"	2	40, 60
7	11c"	2	45, 50, 5[a]

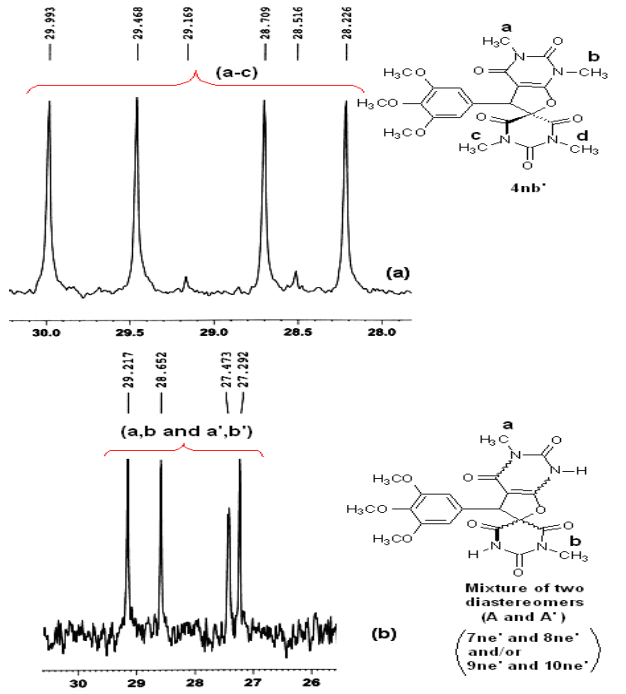
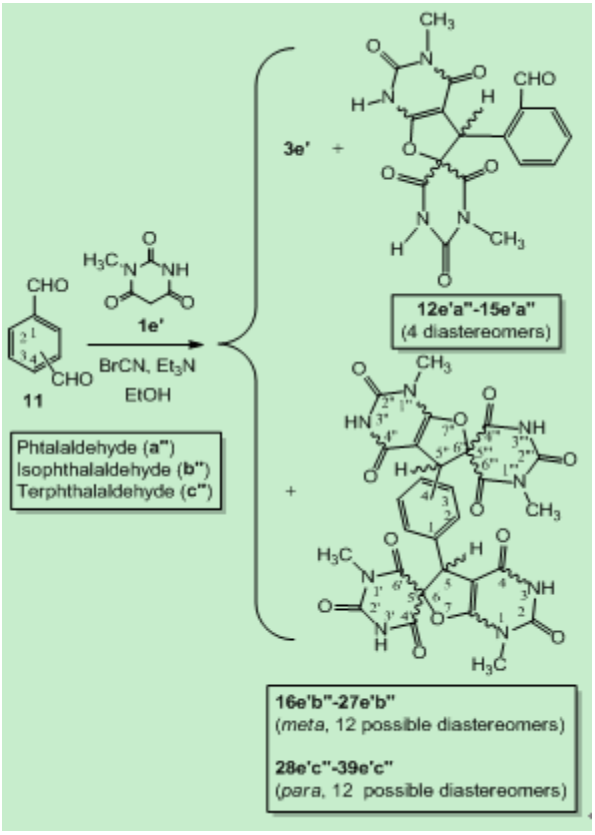


Fig. 4 Comparison of the expanded ^{13}C NMR spectra of N-CH_3 aliphatic regions of **4nb'** (a) [33] in $CDCl_3$ and two diastereomeric mixture of **7ne'** and **8ne'** (and/or **9ne'** and **10ne'**) in the presence of L-(+)-TA (b) in DMSO-d_6

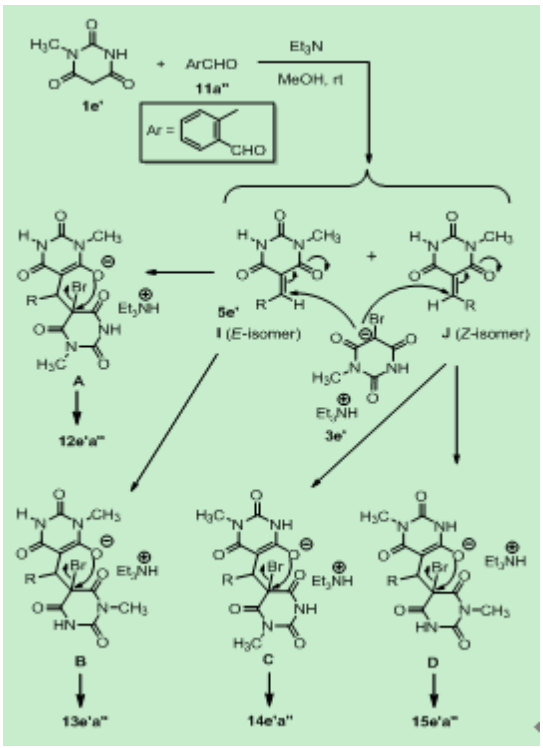
As to the proximate percent of each diastereomer due to C-H peaks overlapping, the new one-pot reaction of **1e'** with BrCN and **11a''-11c''** in the presence of triethylamine afforded diastereomeric mixtures of new class of stable heterocyclic spiro mono- and bis-barbiturates (Scheme 4). Owing to the hindrance effect in the reaction of **11a''**, only one of its aldehyde group was reacted and formed diastereomeric mixture of 2-((5*R*,5'*R*)-1',3-dimethyl- (**12e'a''**), 2-((5*R*,5'*S*)-1',3-dimethyl- (**13e'a''**), 2-((5*R*,5'*R*)-1,1'-dimethyl- (**14e'a''**) and 2-((5*R*,5'*S*)-1, 1'-dimethyl-2, 2', 4, 4', 6'-pentaoxo-2, 2', 3, 3', 4, 4', 5, 6'-octahydro-1*H*, 1'*H*-spiro[furo[2,3-*d*]pyrimidine-6,5'-pyrimidin]-5yl)benzaldehyde (**15e'a''**) (Scheme 4). The reaction of **1e'** with **11b''** and **11c''** were afforded diastereomeric mixture of **16-27e'b''** and **28-39e'c''**, respectively in the presence of BrCN and triethylamine (Scheme 4). The separation of these diastereomers was unsuccessful due to their equal polarity.



Scheme 4 Reaction of **1e'** with **11a''-c''** and BrCN in the presence of triethylamine

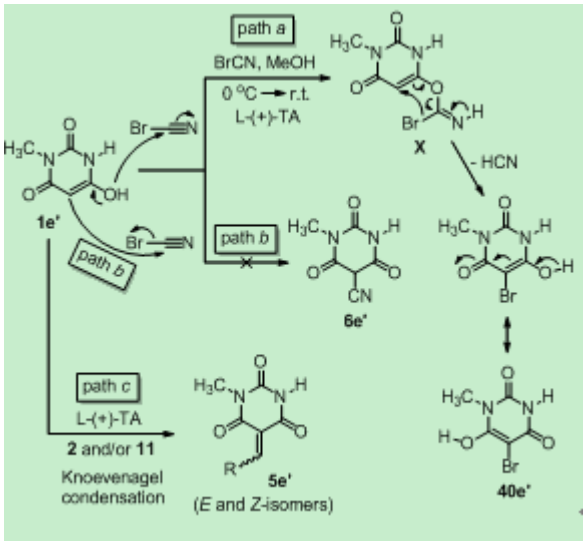
Representatively, the proposed mechanism of the formation of four diastereomers **12e'a''-15e'a''** under basic condition is shown in Scheme 5.

First, the Knoevenagel condensation of **1e'** with phthalaldehyde **11a''** as representative afforded two geometric: *E*- (**I**) and *Z*-isomers (**J**) of **5e'**. Michael addition of **3e'** to **I** and **J** obtained intermediates **A-D**, respectively. Unfortunately, all attempts failed to separate or characterize these intermediates (**A-D**). Finally, intramolecular nucleophilic attack of oxygen anion to the carbon atom (*O*-attack) afforded **12e'a''-15e'a''** in good yield and also triethylammonium hydrobromide salt (Scheme 5). Similarly, as mentioned above, **3e'** also has major role in the reaction with **11a''-11c''** for the synthesis of possible distereomeric mixture of bis-spiro barbiturates (**12-39**) under the same condition (Scheme 5).



Scheme 5 Proposed mechanism for the preparation of possible four diastereomers of **12e'a''-15e'a''** in the presence of triethylamine

Similar to role of **3e'**, the 5-bromo-1-methyl BA (**40e'**) also plays a major role (act either as nucleophile or as electrophile) for the synthesis of mono- and bis-spiro compounds from the one-pot reaction of mono- and dialdehydes with **1a'-1e'** and BrCN in the presence of L-(+)-TA. A proposed mechanism for the formation of **40e'** is shown in Scheme 6.

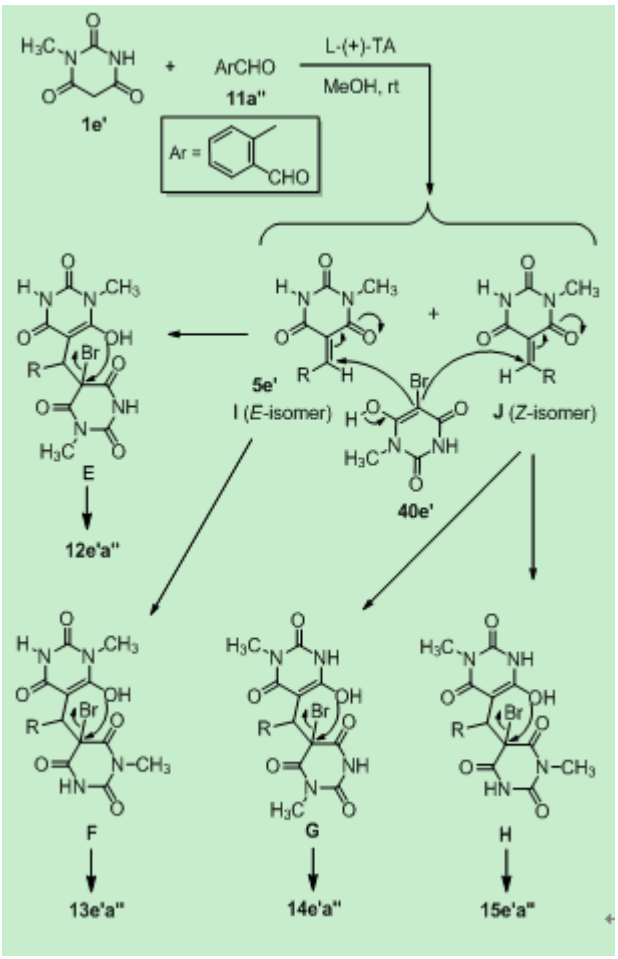


Scheme 6 Proposed mechanism for the preparation of **5e'** and **40e'**

It is reasonable to assume that the enolic form of **1e'** reacted with BrCN formed an intermediate (**X**). Intramolecular rearrangement of **X** [36] afforded **40e'** followed by loss of HCN (path *a*). No **40e'** was isolated in the reaction mixture. For this reason, we also performed the reaction of **1a'-1e'** with BrCN in the absence of aldehyde **2** in the presence of L-(+)-TA. The **40a'-e'** was obtained in good yield. In parallel, as a competition reaction, the Knoevenagel condensation of **1e'**

with **2** and/or **11** was also occurred (path *c*). No 1-methyl-2, 4, 6-trioxohexahydropyrimidine-5-carbonitrile (**6e'**) was observed in these reactions (in the presence of both triethylamine and/or L-(+)-TA) so we concluded that no path *b* was occurred (Scheme 6).

Representatively, the proposed mechanism of the formation of **12e'a''-15e'a''** is shown in Scheme 7 under acidic condition (L-(+)-TA).



Scheme 7 Representatively, proposed mechanism for the preparation of **12e'a''-15e'a''** in the presence of L-(+)-TA

First, the Knoevenagel condensation of **1e'** with phthalaldehyde (**11a''**) afforded the mixture of *E*- and *Z*-isomers (**I** and **J** forms, respectively) then Michael addition of **40e'** to β-carbon position of **I** and/or **J** as an α,β-unsaturated carbonyl compound gave intermediates **E-H**. Unfortunately, all attempts failed to separate or characterize **E-H**. Finally, intramolecular nucleophilic attack of OH group to the carbon atom (pushing the bromide ion out) produced **12e'a''-15e'a''** in good yield (Scheme 7). For instance, 5-bromo-1, 3-dimethyl BA (**40b'**) was reported to react with another unsaturated carbon-carbon double bond to form 5-spirobarbiturate system under basic condition [38, 39]. Recently, Elinson *et al* has also been reported the structures of **4b'** in the reaction of DMBA **1b'** with aldehydes in the presence of bromine under basic condition (EtONa/EtOH) [40].

The reaction of aromatic aldehydes possessing strong electron donor and bulky hindered substituents such as 4-dimethylamino benzaldehyde (**2r**) and 9-antharene carbaldehyde (**2s**) exclusively were afforded Knoevenagel adducts, respectively in the reaction with 1-MBA **1e'** and BrCN in the presence of triethylamine and/or L-(+)-TA (*E*- and *Z*-isomers of **5re'** and **5se'**, respectively).

III. EXPERIMENTAL: THE GENERAL PROCEDURES

The drawing and nomenclature of compounds were done 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 **1e'** was synthesized and purified in our laboratory as described in the literature previously [19]. The BrCN was synthesized based on reported references [41]. Compounds **1a'-1d'**, L-(+)-TA and used solvents purchased from Merck without further purification.

General procedures for the preparation of **3e'**, **5re'**, **5se'**, **7ae'-7qe' through 10ae'-10qe'**, **12e'a''-15e'a''** and **11e'b''-11e'c''**.

The physical and spectral data of the selected compounds from **3e'**, **5re'**, **5se'**, **7ae'-7qe' through 10ae'-10qe'**, **40e'**, **12e'a''-15e'a''** and **11e'c''** are the following as representatives.

In a 10 mL with Teflon-faced screw cap tube equipped by a magnetically stirrer, dissolved 0.136 g (0.96 mmol) 1-methyl barbituric acid, 0.072 g (0.48 mmol) 3-nitrobenzaldehyde and 0.8 g L-(+)-tartaric acid in 10 mL methanol and then 0.06 g (0.48 mmol) BrCN was added into solution at 0 ℃. The reaction mixture was stirred for 2 h at 0 ℃ to room temperature. The Teflon-faced screw cap tube prevented the vaporization of BrCN during the reaction time. The progression of reaction was monitored by thin layer chromatography (AcOEt:AcOH/ 80:20/ v:v). After a few minutes, the crystalline white solid precipitate, filtered off, washed with few mL methanol and dried. (0.05 g, 55% yield).

1-Methylpyrimidine-(1*H*, 3*H*, 5*H*)-2, 4, 6-trione (1e') [37]: White solid; m.p. 132 ℃; FT-IR (KBr) 3423, 3194, 3084, 2922, 2850, 1759, 1687, 1455, 1376, 1356, 1281 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.03 (s, 3H), 2.57 (s, 2H), 11.30 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 167.4, 166.9, 152.3, 77.7, 27.3.

Triethylammonium-5-bromo-2,4,6-trioxohexahydropyrimidin-5-ide (3a') [33, 34]: White solid (50%); mp = 155-158 ℃ (decomps.); FT-IR (KBr) 3130, 2985, 2816, 1658, 603, 524 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.16 (t, 9H), 3.08 (q, 6H), 8.93 (bs, 1H), 9.38 (s, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) 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-5-bromo-4,6-dioxo-2-thioxohexahydropyrimidin-5-ide (3c') [33,34]: White solid (50%); mp = 159-161 °C; FT-IR (KBr) 3408, 3070, 2975, 2937, 2677, 1648, 1612, 590, 526 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 1.16 (t, 9H), 3.07 (q, 6H), 10.17 (bs, 1H), 10.35 (bs, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) 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 %.

1,1'-Dimethyl-5-(3-nitrophenyl)-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 (One distinct diastereomer among 7ce'-10ce'): White solid; FT-IR (KBr) 3428, 3024, 2027, 2856, 2814, 1736, 1707, 1655, 1528, 1356 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 2.35 (3, 3H), 3.05 (s, 3H), 5.26 (s, 1H), 7.61 (m, 2H), 8.07 (s, 1H), 8.15 (m, 1H), 11.18 (s, 1H), 11.97 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 165.7, 164.8, 164.1, 159.2, 151.0, 149.8, 147.9, 137.6, 136.0, 130.1, 124.0, 123.7, 90.0, 85.9, 54.8, 29.3, 27.4.

4-(1,1'-Dimethyl-2,2',4,4',6'-pentaoxo-2,2',3,3',4,4',5,6'-octahydro-1*H*,1'*H*-spiro[furo[2,3-*d*]pyrimidine-6,5'-pyrimidin]-5-yl)benzonitrile (Mixture of two diastereomers among 7ee'-10ee'): White solid; m.p. 264 °C (decomps.); FT-IR (KBr) 3433, 3050, 2229, 1702, 1630, 1465 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 2.38 (s, 3H), 3.08 (s, 3H), 5.08, 5.12 (2s, 1H), 7.37 (m, 2H), 7.38 (d, 2H, J = 8.1 Hz), 7.78 (d, 2H, J = 8.1 Hz), 11.18, (s, 1H), 11.95 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 165.9, 165.8, 164.7, 164.1, 163.9, 163.5, 159.1, 151.2, 151.0, 149.8, 140.8, 132.4, 130.4, 130.3, 118.9, 111.7, 90.0, 89.8, 86.0, 84.9, 55.5, 29.3, 27.4, 27.3.

5-(4-Bromophenyl)-1,1'-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 (Mixture of three diastereomers among 7fe'-10fe'): White solid; m.p. 251 °C (decomps.); FT-IR (KBr) 3406, 3051, 2868, 2816, 1736, 1706, 1658, 1589, 1526, 1459, 1375 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 2.47 (s, 3H), 3.04 (s, 3H), 4.93, 4.98, 5.01 (3s, 1H), 7.10 (d, 2H, J = 8.4 Hz), 7.49 (d, 2H, J = 8.4 Hz), 11.16, 11.92, 13.0 (3s, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 155.2, 166.0, 164.5, 164.1, 159.1, 151.0, 150.0, 149.9, 134.5, 131.4, 131.3, 122.3, 122.2, 90.2, 86.2, 55.6, 29.3, 27.4, 27.3.

5-(3-Hydroxy-4-methoxyphenyl)-1,1'-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 (One distinct diastereomer among 7me'-10me'): Yellow solid; m.p. 210 °C (decomps.); FT-IR (KBr) 3600, 3446, 3206, 3016, 2819, 1707, 1654, 1516, 1445, 1379 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 2.43 (s, 3H), 2.47 (s, 3H), 3.71 (s, 3H), 4.74 (s, 1H), 6.47 (s, 2H), 6.78 (s, 1H), 8.96 (s, 1H), 11.15 (s, 1H), 11.85 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 166.4, 164.3, 164.1, 159.1, 151.0, 150.0, 148.3, 146.6, 127.0, 119.9, 115.9, 112.0, 90.6, 86.5, 56.6, 56.1, 29.2, 27.5.

1,1'-Dimethyl-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 (Mixture of two diastereomers among 7ne'-10ne'): White solid; m.p. 294 °C (decomps.); FT-IR (KBr) 3432, 3009 (CH-ar.), 2841, 1706, 1653, 1124 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 2.39 (s, 3H), 3.06 (s, 3H), 3.14 (s, 3H), 3.61 (s, 3H), 3.67 (s, 6H), 4.83, 4.86, 4.88, 4.91 (4s, 1H, 4CH-aliph.), 6.44, 6.47 (s, 2H, Ph), 11.13, 11.32, 11.35, 11.87, 11.90, 12.95 (6s, 2H, 2NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 167.0, 166.9, 166.2, 166.1, 164.4, 163.7, 163.6, 163.1, 159.7, 159.1, 153.0, 152.9, 151.3, 151.1, 150.3, 150.2, 150.1, 138.1, 130.4, 130.3, 130.2, 107.0, 106.7, 90.6, 85.8, 60.5, 60.4, 57.2, 57.1, 56.4, 29.2, 28.7, 27.5, 27.3.

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'**) [36]: White solid (60%); mp = 205-207 °C; FT-IR (KBr) 3425, 3050, 2926, 2848, 1712, 1687, 1666, 1382 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.67 (s, 3H), 3.32 (s, 6H), 3.42 (s, 3H), 3.53 (s, 3H), 3.79 (s, 3H), 3.81 (s, 3H), 4.84 (s, 1H), 6.25 (s, 2H.); ^{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-(1',3-Dimethyl-2,2',4,4',6'-pentaoxo-2,2',3,3',4,4',5,6'-octahydro-1*H*,1'*H*-spiro[furo[2,3-*d*]pyrimidine-6,5'-pyrimidin]-5-yl)phenyl)-1,1'-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 (Mixture of three diastereomers among 28e'c''-39e'c''): White solid; m.p. 232 °C (decomps.); FT-IR (KBr) 3470, 3047, 2825, 1706, 1650, 1550, 1513, 1441, 1378, 1022, 757, 567 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 2.32 (s, 3H), 3.03 (s, 3H), 3.05 (s, 3H), 3.29 (s, 3H), 4.84, 4.89, 4.93 (s, 2H, mixture of at least three diastereomers and equilibrium mixtures of tautomers), 7.00 (m, 4H), 10.76, 11.43 (bs, 1H), 11.13 (s, 1H), 11.82 (bs, 1H), 12.98 (bs, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) 167.2, 165.1, 164.4, 163.3, 159.6, 159.1151.4, 151.0, 150.0, 135.0, 129.0, 128.8, 90.0, 49.0, 46.1, 29.2, 28.7, 27.27, 27.26.

5-(2-Formylphenyl)-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 (11a'a''): White solid; m.p. = 287 °C (decomps.); FT-IR (KBr) 3224, 2991, 2787 (COH), 2687 (COH), 1736, 1688, 1587 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 5.88 (s, 1H), 7.31 (d, 1H, J=5.7 Hz), 7.59 (m, 2H), 7.95 (d, 1H, J=6.3 Hz), 10.06 (s, 1H), 10.88 (s, 1H), 11.10 (s, 1H), 11.74 (s, 1H), 12.66 (bs, 1H).

5-(2-Formylphenyl)-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 (11b'a''): White solid; m.p. = 388 °C (decomps.); FT-IR (KBr) 3050, 2926, 2854, 2738, 1691, 1518, 1438, 1382 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.64 (s, 3H), 3.31 (s, 3H), 3.46 (s, 3H), 3.50 (s, 3H), 6.10 (s, 1H), 7.39 (d, 1H, J = 7.2 Hz), 7.60 (m, 2H), 7.77 (d, 1H, J = 6.9 Hz), 9.94 (s, 1H, COH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 194.4, 165.6, 163.4, 162.6, 158.6, 151.2, 149.8, 136.0, 134.4, 134.2, 133.6, 131.5, 129.4, 88.6, 86.8, 52.3, 29.9, 29.5, 28.2, 28.2. MS (*m/z*, %) 426 (M^+, 6), 397 (4), 310 (90), 280 (6), 253 (65), 222 (100, base peak), 197 (30), 183 (50),m 156 (15), 138 (16), 111 (10), 83 (18), 69 (80), 58 (60), 53 (28), 43 (28).

2-(1,1',3,3'-Tetraethyl-4,4',6'-trioxo-2,2'-dithioxo-2,2',3,3',4,4',5,6'-octahydro-1*H*,1'*H*-spiro[furo[2,3-*d*]pyrimidine-6,5'-pyrimidine]-5-yl)benzaldehyde (11d'a''):

White solid; m.p. = 212 °C (decomps.); FT-IR (KBr) 3050, 2979, 2930, 2856, 2748, 1738, 1696, 1666, 1493, 1401, 1111 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 0.68 (t, 3H, J = 6.9 Hz), 1.27 (t, 3H, J = 6.9 Hz), 1.37 (t, 3H, J = 6.9 Hz), 1.47 (t, 3H, J = 6.9 Hz), 3.49 (m, 1H), 3.85 (sextet, 1H, J = 6.9 Hz),

4.43-4.67 (m, 6H), 6.34 (s, 1H), 7.36 (d, 1H, *J* = 7.2 Hz), 7.55-7.64 (m, 2H), 7.73 (d, 1H, *J* = 6.6 Hz), 9.92 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 193.7, 177.2, 175.8, 163.8, 162.0, 161.6, 157.0, 136.2, 134.1, 133.8, 133.6, 131.4, 129.4, 91.5, 88.5, 51.9, 45.1, 44.8, 43.7, 43.6, 12.5, 12.1, 11.7, 11.5.

1,3-Bis{[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]-5-yl}benzene (11a'b''): White solid; m.p. 320 °C (decomps.); FT-IR (KBr) 3470, 3047, 2825, 1706, 1441, 1378 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.64, 4.67, 4.70 (s, 2H), 6.94 (s, 1H), 7.03 (m, 2H), 7.17 (m, 1H), 10.31 (bs, 1H (a shoulder at the peak's left side), 10.76, 10.80, 10.84 (1H), 11.56, 11.59 (1H), 12.66 (bs, 1H) (mixture of 3 rotamers); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.2, 165.0, 164.8, 163.7, 160.7, 160.6, 160.3, 151.2, 151.1, 149.2, 135.4, 129.8, 129.7, 128.4, 89.5, 89.4, 86.8, 86.6, 86.5, 55.8, 55.5. MS (*m/z*, %) 606 (M^+, 1), 493 (6), 438 (12), 294 (6), 279 (10), 246 (15), 203 (50), 190 (18), 177 (20), 164 (12), 149 (24), 85 (16), 71 (32), 57 (66), 43 (100, base peak).

1,3-Bis{[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]-5-yl}benzene (11b'b''): White solid; m.p. 251 °C (decomps.); FT-IR (KBr) 3050, 2954, 2926, 2856, 1691, 1515, 1440, 1378, 1041, 753 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.72 (s, 3H), 3.32 (s, 3H), 3.38 (s, 3H), 3.52 (s, 3H), 4.77 (s, 1H), 4.85 (s, 1H), 6.84 (s, 1H), 7.10 (d, 2H, *J* =7.5 Hz), 7.32 (t, 1H, *J* =7.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.4, 162.9, 162.6, 158.2, 151.2, 149.2, 134.6, 134.3, 129.8, 129.3, 129.0, 128.6, 128.2, 89.9, 85.9, 58.5, 30.0, 29.5, 28.9, 28.2.

1,3-Bis{[1,1',3,3'-tetraethyl-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]-5-yl}benzene (11d'b''): White solid; m.p. 342 °C; FT-IR (KBr) 2980, 1741, 1698, 1620), 1491, 1437, 1385 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.19-1.50 (m, 12H), 4.54-4.71 (m, 8H), 4.83 (s, 1H), 6.85 (s, 1H), 7.12 (d, 2H, *J* = 7.8 Hz), 7.29 (t, 1H, *J* = 7.8 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 177.5, 174.6, 163.7, 162.1, 162.0, 161.0, 132.3, 129.3, 127.7, 126.7, 126.6, 124.3, 59.0, 44.6, 44.0, 43.9, 43.6, 12.5, 12.4, 11.8, 11.5.

1,4-Bis{[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]-5-yl}benzene (11a'c''): White solid; m.p. 386 °C (decomps.); FT-IR (KBr) 3448, 3209, 3064, 2833, 1719, 1674, 1411, 1357 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.68, 4.71, 4.74 (3s, 2H), 6.95, 6.99, 7.01 (3s, 4H), 10.54 (bs, 2H), 10.74, 10.77, 10.80 (3s, 2H), 11.58 (s, 2H), 12.58 (bs, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 167.34, 164.8, 163.7, 160.2, 151.2, 149.6, 135.4, 128.9, 89.4, 86.2, 55.4.

1,4-Bis{[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]-5-yl}benzene (11b'c''): White solid; m.p. 364 °C (decomps.); FT-IR (KBr) 3050, 2965, 1712, 1691, 1662, 1517, 1437, 1374 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.59 (s, 3H), 2.66 (s, 3H), 3.29 (s, 3H), 3.30 (s, 3H), 3.41 (s, 3H), 3.52 (s, 3H), 4.87 (s, 1H), 4.90 (s, 1H), 7.045 (s, 2H), 7.054 (s, 2H) (Mixture of two rotamers **3fA** and **3fB**); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.4, 162.8, 158.3, 151.2, 149.5, 134.6, 128.8, 89.9, 85.1, 58.5, 30.0, 29.5, 28.7, 28.5.

5-(4-(1',3-Dimethyl-2,2',4,4',6'-pentaoxo-2,2',3,3',4,4',5,6'-octahydro-1*H*,1'*H*-spiro[furo[2,3-*d*]pyrimidine-6,5'-pyrimidin]-5-yl)phenyl)-1,1'-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 (11e'c''): White solid; m.p. 232 °C (decomps.); FT-IR (KBr) 3470, 3047, 2825, 1706, 1650, 1550, 1513, 1441, 1378, 1022, 757, 567 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.32 (s, 3H), 3.03 (s, 3H), 3.05 (s, 3H), 3.29 (s, 3H), 4.84, 4.89, 4.93 (s, 2H, mixture of at least three diastereomers and equilibrium mixtures of tautomers), 7.00 (m, 4H), 10.76, 11.43 (bs, 1H), 11.13 (s, 1H), 11.82 (bs, 1H), 12.98 (bs, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 167.2, 165.1, 164.4, 163.3, 159.6, 159.1151.4, 151.0, 150.0, 135.0, 129.0, 128.8, 90.0, 49.0, 46.1, 29.2, 28.7, 27.27, 27.26.

(*E* and *Z*)-5-(Anthracen-9-ylmethylene)-1-methylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (5se'): Red solid; FT-IR (KBr) 3421, 3188, 3056, 2857, 1706, 1675, 1582, 1444, 1379, 736 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.89 (s, 3H), 3.26 (s, 3H), 7.50 (m, 8H), 7.92 (m, 4H), 8.12 (d, 4H, *J* = 8.1 Hz), 8.64 (s, 2H), 9.01 (2s, 2H), 11.29 (s, 1H), 11.74 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 162.6, 161.7, 160.6, 160.0, 152.4, 152.3, 151.32, 151.27, 131.0, 130.1, 129.9, 129.1, 128.3, 128.1, 128.0, 126.7, 126.0, 125.7, 28.1, 27.3.

VI. CONCLUSION

In summary, the one-pot reaction of 1-methyl BA as an unsymmetrical barbituric acid with mono- and dialdehydes in the presence of BrCN and triethylamine and/or L-(+)-TA was used to develop an efficient synthetic procedure to prepare diastereomeric mixture of stable mono- and bis-spiro barbiturates. We also concluded that this reaction diastereoselectively was performed in the presence of L-(+)-TA and the number of diastereomers was reduced. Phthalaldehyde was formed mono spiro barbiturate but isophthalaldehyde and terphthalaldehyde were formed bis-spiro barbiturate. The aromatic aldehydes possessing strong electron donor and bulky hindered substituents exclusively were afforded Knoevenagel adducts.

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SUPPLEMENTARY MATERIAL

Full characterization data of **1e'** and compounds derived from one pot reaction of **1e'** with aldehydes **2c**, **2e**, **2f**, **2m**, **2n**, **11a''**, **11b''** and **11c''** are available.

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