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A FACILE ONE-POT SYNTHESIS OF MODEL DIETHYL 6,6'-DIOXOTETRAHYDRO-5,5'-BI(1,2,4-TRIAZINE)-5,5'-DICARBOXYLATES

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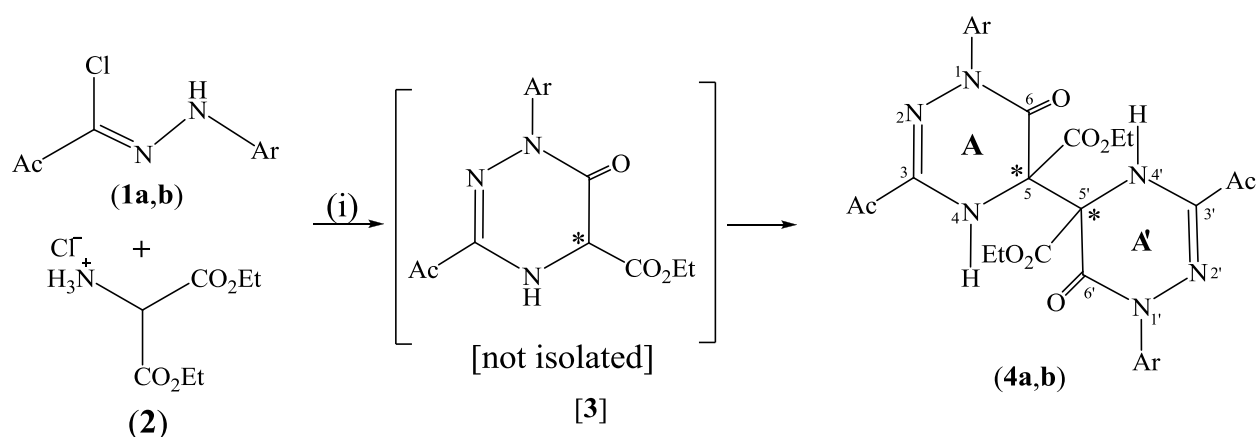
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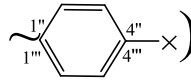
Abstract – The reaction of diethyl aminomalonate with nitrile imine 1,3-dipolar species **1a,b** follows a stereospecific path to deliver the racemic tetrahydro-6,6'-dioxo-5,5'-bi(1,2,4-triazine)-5,5'-dicarboxylates **4a,b**, whilst the corresponding diastereomeric *meso* forms (5*R*, 5'*S*) could not be detected in the reaction product. Structural assignments for these novel heterocyclic dimers are based on microanalytical and spectral (MS, NMR) data, and further confirmed by X-ray diffraction analysis of single crystal for **4a**.

4,5-Dihydro-1,2,4-triazin-6-ones constitute valuable heterocycles as scaffolds for combinatorial chemistry. They possess significant biological activities such as antimicrobial, antibacterial, fungicide, pesticide, herbicide, crop protection and blood platelet aggregation inhibition.¹⁻³ Some derivatives were also reported to exhibit antitumor activity against leukemia / lymphoma, ovarian cancer, small and large lung cancer cells, and breast cancer.^{4,5}

The reaction of α -amino esters with hydrazonoyl chlorides, precursors of nitrile imine 1,3-dipolar species, was reported⁶ to constitute an efficient one-pot synthesis of chiral 4,5-dihydro-1,2,4-triazin-6-ones having a wide variety of substituents appended at N-1, C-3 and C-5 positions. Those triazin-6-ones, incorporating an alkoxy carbonyl group at carbon-5 locus (exemplified by **3** / see Scheme 1) are hitherto undescribed in the literature; such ester moiety is convertible to the carboxy group which, in turn, can be manipulated for the installation of carbon and / or hetero-atom substituents where desired, and thus might lead to enhancement of their biological activities. Modeled on our previous findings,⁶ we envisaged that employment of

aminomalonic ester **2**, in place of α -amino esters, in the reaction with hydrazoneyl chlorides **1a,b**, would lead to the respective targeted 6-oxo-4,5-dihydro-1,2,4-triazine-5-carboxylates **3a,b** (see Scheme 1). In the present work this expectation was, however, not realized and the main isolable reaction products were identified as the respective 6,6'-dioxo-tetrahydro-5,5'-bi(1,2,4-triazine)-5,5'-dicarboxylates (**4a,b**), dimers of their presumed monomeric precursors **3a,b** (Scheme 1). Herein, we wish to report on the synthesis, spectral and stereochemical properties of model bis-triazazine derivatives **4a,b**, accessible *via* a facile one-pot synthetic route outlined in Scheme 1.



compounds **1**, **3** and **4** : (Ar = )

(i) NEt₃, EtOH / 0-2 °C, 2 h; then rt, 10 h

a (x = Cl); **b** (x = Br)

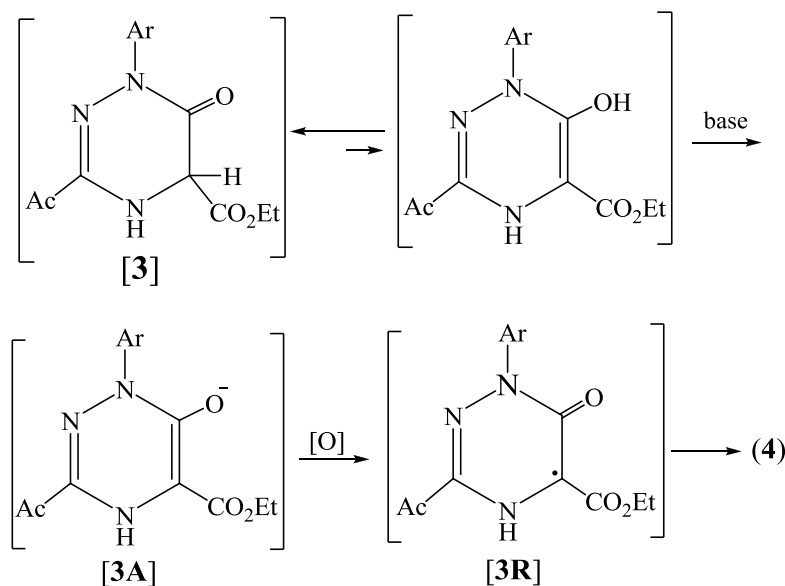
Scheme 1. Synthesis of 6,6'-dioxo-tetrahydro-5,5'-bi(1,2,4-triazine)-5,5'-dicarboxylates **4a,b**

In the presence of triethylamine, the reaction of diethyl aminomalonate **2** with *N*-arylhydrazoneyl chlorides **1a,b** is envisaged to yield the respective ethyl 6-oxo-4,5-dihydro-1,2,4-triazine-5-carboxylates (**3a,b**) as stable cyclo-condensation end products (Scheme 1). However, the ¹H- and ¹³C-NMR spectral data of the isolable products lack the methine C(5)-H proton's signal as well as the ¹³C(5)-H carbon signal (absent in the DEPT experiments) that are characteristic of **3a,b**. Conversely, the ¹³C-NMR spectra revealed the presence of an additional low intensity signal (absent in the DEPT experiments) at $\delta \approx 65$ ppm; this signal is tentatively assigned to the equivalent quaternary hetero-ring carbons (C-5 / C-5') of the presumed structure for the dimeric products **4a,b** (Scheme 1). The MS and NMR spectral data and microanalyses for the new compounds **4a,b** are in accordance with the assigned structures; details are given in the Experimental section. Each of the dimeric products **4a,b** incorporates two identical stereocenters (C-5 and C-5') that are constructed from symmetric reactants (**1a,b** and **2**) in symmetric environment. Accordingly, each product is optically inactive, being either a racemate or a meso form; this is inferred from the NMR spectra of **4a,b** whereby signal doubling was not observed indicating that the different protons and carbons associated with the heteroring A are virtually equivalent, but not diastereomeric, to their counterparts in ring A'.

The stereochemical aspects of **4a** were indicated by $^1\text{H-NMR}$ using europium(III) tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] as the chiral lanthanide shift reagent (LSR).⁶⁻⁸ After addition of $\text{Eu}(\text{hfc})_3$ (molar ratio of $[\text{Eu}(\text{hfc})_3] / [\text{substrate}] = 0.64$), the signal of the C(3)-acetyl methyl protons (s, $\delta = 2.48$ ppm) was resolved into two diastereotopic singlets (at 2.54 and 2.56 ppm) of equal integrated peak areas. Likewise, the methyl (t, $\delta = 1.27$ ppm) and methylene (q, $\delta = 4.28$ ppm) protons' signals belonging to the C(5)-ethyl ester group, were resolved into two diastereotopic triplets (1.28 and 1.29 ppm) and quartets (4.31 and 4.34 ppm), respectively. These results strongly support that **4a** is a racemic mixture: (*5R,5'R*) + (*5S,5'S*). Hence, it can be concluded that the reaction of aminomalonate with nitrile imines proceeds in a stereospecific manner to deliver *racemic* tetrahydro-5,5'-bi(1,2,4-triazinones), while the diastereomeric (*5R,5'S*) *meso* counterparts were not detected. An additional diagnostic criterion for the dimeric structure came from the MS spectral data. Thus, the measured HRMS (ESI) spectrum of **4a** displayed, in the molecular ion region, an isotopic cluster of three distinct peaks: $[\text{M}+\text{H}]$, $[\text{M}+\text{H}+2]$ and $[\text{M}+\text{H}+4]$ with relative intensity ratios (relative abundance) of 9 : 6 : 1, respectively, indicative of the presence of two chlorine atoms in the molecule, and is supportive of the dimeric structure for **4a**. Corresponding isotopic peaks are also displayed in the MS of **4b** with relative ratios of 1 : 2 : 1, indicative of the presence of two bromine atoms in **4b**. Eventually, the cyclic products (from **2** and **1a,b**) were identified as 1,1'-diaryl-6,6'-dioxo-tetrahydro-5,5'-bi(1,2,4-triazine)-5,5'-dicarboxylates (**4a,b**) as evidenced from their elemental analyses, MS, ^1H - and ^{13}C - NMR spectral data, and confirmed by single crystal X-ray structure determination for **4a** (Table 1 and Table 2; Figure 1 and Figure 2 / *vide infra*).

The production of the dimeric heterocycles **4a,b** is probably initiated by the formation of the monomeric 6-oxo-4,5-dihydro-1,2,4-triazine-5-carboxylates **4a,b**; the latter transient intermediates are then transformed into **4a,b**, for which a plausible radical-mediated pathway involving a single electron transfer is postulated in the annexed mechanism (Scheme 2).

The instability of **3** in basic media might be due to the tendency of their resonance stabilized enolate anions [**3A**] to form radical species [**3R**] by the action of oxygen in basic solution; the resulting relatively stable radicals [**3R**] are liable to experience dimerization, thereby producing the respective dimeric products **4** (Scheme 2). This mode of oxidative dimerization is modeled on, and reminiscent of the conversion of indoxyl to the indigo dyestuff by the action of oxygen in basic solution, and for which an eminently reasonable mechanism, was previously suggested for the conversion of indoxyl anion to indoxyl radical, followed by radical coupling to produce the leucoindigo (which is further oxidized to indigo).⁹



Scheme 2. Proposed mechanism for the formation of the dimeric compounds **4a,b**

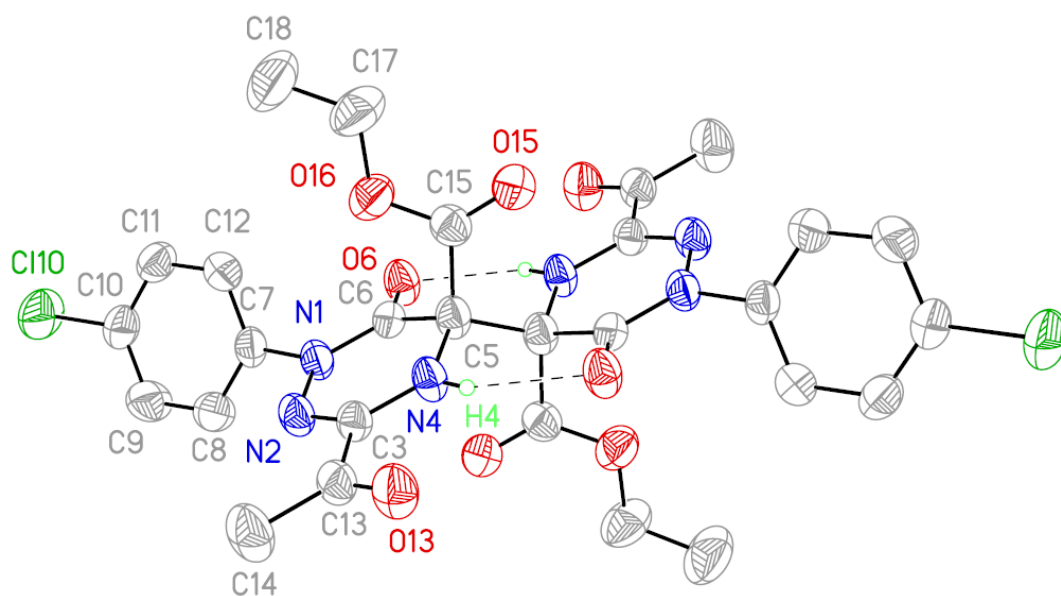


Figure 1. Molecular structure of (\pm) -**4a**. Only atoms of the asymmetric unit are labeled. Hydrogen bonding interactions are represented by dashed lines. Hydrogen atoms are omitted for clarity except those involved in the N-H...O hydrogen bonding interactions.

Molecular structure of 4a. A crystal structure determination was performed to confirm the structure of **4a** (and by inference that of **4b**). A summary of data collection and refinement parameters is given in Table 1, while selected bond lengths and angles are provided in Table 2. The molecular structure of **4a** in the crystal is displayed in Figure 1. The asymmetric unit of **4a** contains one half molecules, the second half of **4a** is generated by inversion through a center located at the middle of C5–C5A bond (Figure 1), where C5A

Table 1. Summary of data collection and refinement parameters for (±)- **4a**

Empirical formula	$C_{28} H_{26} Cl_2 N_6 O_8$
Formula weight	645.45
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	$P -1$
Unit cell dimensions	$a = 7.9036(14) \text{ \AA}$ $\alpha = 68.75(2)^\circ$ $b = 9.6960(19) \text{ \AA}$ $\beta = 81.980(18)^\circ$ $c = 11.145(3) \text{ \AA}$ $\gamma = 73.981(16)^\circ$
Volume	$764.4(3) \text{ \AA}^3$
Z	1
Density (calculated)	1.402 g / cm^3
Absorption coefficient (μ)	0.271 mm^{-1}
F(000)	334
Theta range for data collection	3.09 to 25.00°
Index ranges hkl	$-8 \leq h \leq 9, -11 \leq k \leq 11, -13 \leq l \leq 13$
Reflections collected	4931
Independent reflections	2699 [$R_{\text{int}}(F^2) = 0.0395$]
Completeness to theta = 25.00°	99.9%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.61885
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2699 / 0 / 203
Goodness-of-fit on F^2	1.027
Final R indices [$I > 2$ sigma (I)]	$R_1^a = 0.0662, wR_2^b = 0.1340$
R indices (all data)	$R_1^a = 0.1339, wR_2^b = 0.1755$
Largest diff. peak and hole	0.216 and $-0.320 \text{ e. \AA}^{-3}$

$$^a R_1 = \frac{\sum ||F_o| - |F_c||}{\sum |F_o|}$$

$$^b wR_2 = \left\{ \frac{\sum w(F_o^2 - F_c^2)^2}{\sum w(F_o^2)^2} \right\}^{1/2}$$

Table 2. Selected bond lengths (Å) and angles (°) for (±)- **4a**

O(6)-C(6)	1.219(4)	C(6)-N(1)-N(2)	126.3(3)
N(1)-C(6)	1.356(5)	C(6)-N(1)-C(7)	120.5(3)
N(1)-N(2)	1.401(4)	C(3)-N(2)-N(1)	114.8(3)
N(1)-C(7)	1.438(5)	C(3)-N(4)-C(5)	124.3(3)
N(2)-C(3)	1.292(4)	C(3)-N(4)-H(4)	120(3)
N(4)-C(3)	1.334(5)	N(2)-C(3)-N(4)	126.4(4)
N(4)-C(5)	1.445(5)	N(2)-C(3)-C(13)	117.9(4)
N(4)-H(4)	0.846(4)	N(4)-C(5)-C(5)#1	111.1(4)
O(15)-C(15)	1.204(5)	N(4)-C(5)-C(6)	109.5(3)
O(13)-C(13)	1.208(4)	C(5)#1-C(5)-C(6)	111.7(4)
C(3)-C(13)	1.494(5)	N(4)-C(5)-C(15)	109.1(3)
C(5)-C(5)#1	1.528(8)	C(5)#1-C(5)-C(15)	108.5(4)
C(5)-C(6)	1.552(5)	C(6)-C(5)-C(15)	106.8(3)
C(5)-C(15)	1.558(6)	N(1)-C(6)-C(5)	117.3(4)

Symmetry transformations used to generate equivalent atoms:

#1 -x, -y + 2, -z + 1

is the symmetry equivalent of C5. The molecular unit of **4a** is stabilized by two intramolecular crystallographically equivalent N4–H4...O6A hydrogen bonding interactions (Figure 1), hydrogen bonding interaction parameters are 0.846 (0.037), 2.080 (0.042), 2.711(0.004) Å and 130.90 (3.77)° for N4–H4 Å, H4...O6A Å, N4...O6A Å and (N4–H4...O6A)°, respectively. These strong hydrogen bond interactions distort the molecular structure; the O6 atom deviates from the plane of the aromatic ring by 0.164 Å toward H4.

Two types of intermolecular interactions connect the molecular units of **4a** to form the final 3D structure; these include the non-classical C–H...O hydrogen bonding interaction and C (carbonyl)...O interactions. C15 (carbonyl)...O13 distance is 3.154 Å which is 0.07 Å less than the sum of van der Waals radii; C (carbonyl)...O interactions collaborate with C14–H14A...O15 to form chain structures run parallel to the *a*-axis (Figure 2). C14–H14A...O15 hydrogen bonding interactions are 2.651, 3.472 and 143.79 for H14A...O15, C14...O15 and C14–H14A...O15, respectively.¹⁰

In conclusion, construction of carbon-carbon sigma bonds *via* oxidative cross-coupling of sp³-hybridized C–H bonds is of great interest and has been achieved using transition metal salts and / or oxidants.¹¹ Dimers of carbonyl compounds have been reported in their oxidation by high valent metal salts in the absence of radical trapping agents.¹² The development of new methodologies in cross-coupling reactions using C–H bonds as substrates is welcomed. Noticeably, the reaction presented here is a special case of metal-free and

oxidant-free cross-dehydrogenative coupling of sp^3 -hybridized C-H bonds under mild conditions whereby the transformation of reactants **1** and **2** into dimers **4** (Scheme 1) constructs three consecutive HN=C=N, ArN=C=O and C₅-C_{5'} sigma bonds in one-pot operation. The scope, stereochemistry, and synthetic applications of this intermolecular oxidative dimerization sequence are currently under investigation.

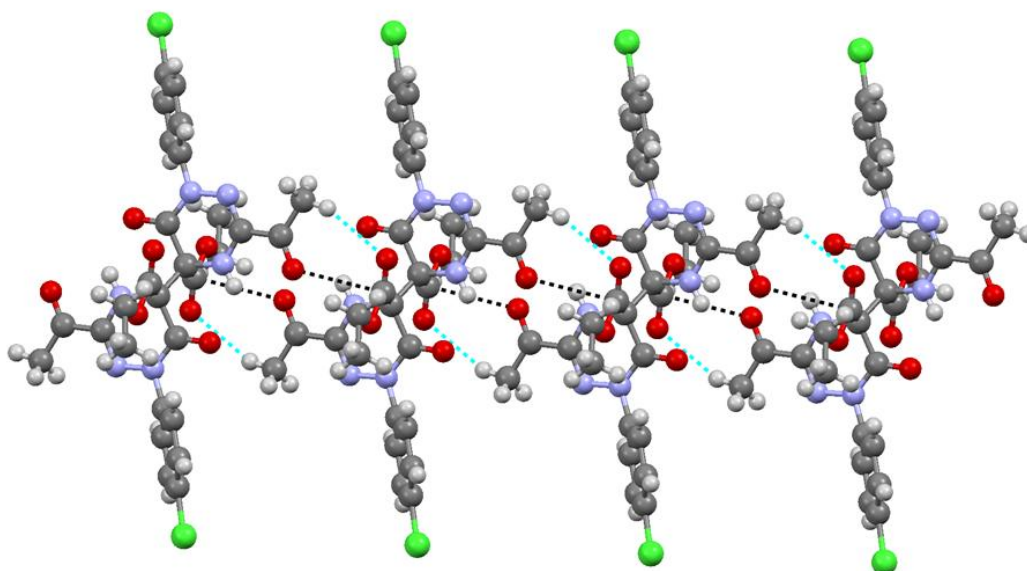


Figure 2. Chain Structure of (±)- **4a**. C15 (carbonyl)...O13 and C-H14...O15 interactions are represented by black and blue dotted lines, respectively.

EXPERIMENTAL

The following chemicals, purchased from Acros, were used in this study: diethyl aminomalonate, 3-chloro-2,4-pentanedione, *p*-bromoaniline and *p*-chloroaniline. Melting points were determined on a Gallenkamp electrothermal melting-temperature apparatus in open capillary tubes. Elemental analyses were performed on a Euro Vector elemental analyzer, model EA 3000. ¹H- and ¹³C-NMR spectra were recorded on a 500 MHz spectrometer (Bruker Avance-III), with TMS as the internal standard. Chemical shifts are expressed in δ units; *J* values for ¹H-¹H coupling constants are given in Hertz. High resolution mass spectra (HRMS) were acquired (in positive mode) using the electrospray ion trap (ESI) technique by collision-induced dissociation on a Bruker APEX-4 (7 Tesla) instrument. The samples were dissolved in dichloromethane, diluted in spray solution (methanol-water 1 : 1 v/v + 0.1 % formic acid) and infused using a syringe pump with a flow rate of 2 μ L / min. External calibration was conducted using arginine cluster in a mass range $m/z = 175 - 871$.

***N'*-Aryl-2-oxopropanehydrazonoyl chlorides (1a,b).** These hydrazonoyl chlorides, employed in this

study, were prepared *via* the Japp-Klingemann reaction¹³ involving direct coupling interaction between the appropriate arenediazonium chloride and 3-chloro-2,4-pentanedione.^{6,14} The melting points, as given below, are in accordance with the literature values (not given here):

N'-(4-chlorophenyl)-2-oxopropanehydrazonoyl chloride (**1a**),^{6,14,15} mp 178–179 °C;

N'-(4-bromophenyl)-2-oxopropanehydrazonoyl chloride (**1b**),^{16,17} mp 166–167 °C.

General procedure for the synthesis of diethyl 1,1'-diaryl-6,6'-dioxo-tetrahydro-5,5'-bi(1,2,4-triazine)-5,5'-dicarboxylates (4a,b). To a solution of the appropriate hydrazonoyl chloride (**1a,b** / 0.01 mole) in EtOH (40 mL) was added a solution of triethylamine [(5 g), 0.05 mole] in EtOH (10 mL). After that, diethyl aminomalonate hydrochloride **2** [(2.54 g), 0.012 mole] in EtOH (20 mL), was added to the reaction mixture. Stirring was continued at ~ 0-5 °C for 2 h, and then at rt for 12 h. The reaction mixture was then diluted with cold H₂O (100 mL), the resulting solid product was collected by suction filtration, washed with cold water (2 × 20 mL), dried, and recrystallized from EtOH, or CHCl₃ / *n*-hexane.

(±) **Diethyl 3,3'-diacetyl-1,1'-bi(4-chlorophenyl)-6,6'-dioxo-4,4',5,5'-tetrahydro-5,5'-bi(1,2,4-triazine)-5,5'-dicarboxylate (4a).** Yield 74%; mp 192 – 193 °C. ¹H NMR (500 MHz, CDCl₃): δ = 1.27 (t, *J* = 7 Hz, 6H, 2 CH₃CH₂O), 2.48 (s, 6H, 2 CH₃C=O), 4.28 (q, *J* = 7 Hz, 4H, 2 OCH₂Me), 7.46 (d, *J* = 8.5 Hz, 4H, 3''-H, 5''-H / 3'''-H, 5'''-H), 7.57 (d, *J* = 8.5 Hz, 4H, 2''-H, 6''-H / 2'''-H, 6'''-H), 8.37 (br s, 2H, N(4)-H / N(4')-H, exchangeable with D₂O). ¹³C NMR (125 MHz, CDCl₃): δ = 13.9 (2 CH₃CH₂O), 23.8 (2 CH₃C=O), 63.6 (2 OCH₂Me), 65.1 (C-5 / C-5'), 126.4 (C-2'', C-6'' / C-2''', C-6'''), 129.0 (C-3'', C-5'' / C-3''', C-5'''), 133.3 (C-4'' / C-4'''), 138.9 (C-1'' / C-1'''), 139.1 (C-3 / C-3'), 158.1 (C-6 / C-6'), 166.7 (2 CO₂Et), 191.5 (2 Me-C=O). HRMS (ESI): *m/z* Calcd. for C₂₈H₂₇³⁵Cl₂N₆O₈, [M+H]⁺: 645.12619, found: 645.12634. Calcd. for C₂₈H₂₇³⁵Cl³⁷ClN₆O₈, [M+2+H]⁺: 647.12408, found: 647.12404. Calcd. for C₂₈H₂₇³⁷Cl₂N₆O₈, [M+4+H]⁺: 649.11910, found: 649.11895. Calcd. for C₂₈H₂₆³⁵Cl₂N₆O₈Na, [M+Na]⁺: 667.10814, found: 667.10847. Calcd. for C₂₈H₂₆³⁵Cl³⁷ClN₆O₈Na, [M+2+Na]⁺: 669.10602, found: 669.10649. Calcd. for C₂₈H₂₆³⁷Cl₂N₆O₈Na, [M+4+Na]⁺: 671.12144, found: 671.12157. Anal. Calcd for C₂₈H₂₆Cl₂N₆O₈ (645.45): C, 52.10; H, 4.06; Cl, 10.99; N, 13.02. Found: C, 52.18; H, 3.98; Cl, 10.82; N, 13.10.

(±) **Diethyl 3,3'-diacetyl-1,1'-bi(4-bromophenyl)-6,6'-dioxo-4,4',5,5'-tetrahydro-5,5'-bi(1,2,4-triazine)-5,5'-dicarboxylate (4b).** Yield 76%; mp 198 - 200 °C. ¹H NMR (500 MHz, CDCl₃): δ = 1.27 (t, *J* = 7.1 Hz, 6H, 2CH₃CH₂O), 2.48 (s, 6H, 2CH₃C=O), 4.28 (q, *J* = 7.1 Hz, 4H, 2 OCH₂Me), 7.52 (d, *J* = 8.6 Hz, 4H, 2''-H, 6''-H / 2'''-H, 6'''-H), 7.61 (d, *J* = 8.6 Hz, 4H, 3''-H, 5''-H / 3'''-H, 5'''-H), 8.36 (br s, 2H, N(4)-H / N(4')-H, exchangeable with D₂O). ¹³C NMR (125 MHz, CDCl₃): δ = 13.9 (2 CH₃CH₂O), 23.8 (2 CH₃C=O), 63.6 (2 OCH₂Me), 65.1 (C-5 / C-5'), 121.3 (C-4'' / C-4'''), 126.7 (C-2'', C-6'' / C-2''', C-6'''), 131.9 (C-3'', C-5'' / C-3''', C-5'''), 139.1 (C-1'' / C-1'''), 139.4 (C-3 / C-3'), 158.1 (C-6 / C-6'), 166.7 (2

CO₂Et), 191.5 (2 Me-C=O). HRMS (ESI): *m/z* Calcd. for C₂₈H₂₇⁷⁹Br₂ N₆O₈, [M+H]⁺: 733.02516, found: 733.02448. Calcd. for C₂₈H₂₇⁷⁹Br ⁸¹BrN₆O₈, [M+2+H]⁺: 735.02338, found: 735.02268. Calcd. for C₂₈H₂₇⁸¹Br₂ N₆O₈, [M+4+H]⁺: 737.02204, found: 737.02039. Calcd. for C₂₈H₂₆⁷⁹Br₂N₆O₈Na, [M+Na]⁺: 755.00711, found: 755.00617. Calcd. for C₂₈H₂₆⁷⁹Br ⁸¹BrN₆O₈Na, [M+2+Na]⁺: 757.00532, found: 757.00486. Calcd. for C₂₈H₂₆⁸¹Br₂ N₆O₈Na, [M+4+Na]⁺: 759.00398, found: 759.00398. Anal. Calcd for C₂₈H₂₆Br₂N₆O₈ (734.35): C, 45.80; H, 3.57; Br, 21.76; N, 11.44. Found: C, 45.62; H, 3.51; Br, 21.54; N, 11.27.

X-Ray structure analysis of (±)- 4a. Crystals were grown by allowing a clear hot solution of (±)- **4a** in EtOH in an open vessel to stand at room temperature for 4 – 5 days. A suitable needle-like slightly yellowish crystal, with approximate dimensions of 0.15 x 0.1 x 0.05 mm³, was epoxy mounted on a glass fiber. Data were collected at room temperature (293 K) using an Oxford Xcalibur diffractometer. Data were acquired and processed to give SHELX-format-hkl files using CrysAlisPro software.¹⁸ Cell Parameters were determined and refined using CrysAlisPro.¹⁸ A multi-scan absorption correction was applied with minimum and maximum transmission factors of 1.00000 and 0.61885, respectively. The structure was solved by Direct Methods and refined by full-matrix least-squares on *F*².¹⁹ All nonhydrogen atoms were refined anisotropically with the hydrogen atoms placed on the calculated positions using riding model, except H4 (Figure 1) which was found using Fourier difference maps and were refined isotropically. Data collection parameters and refinement results are given in Table 1. CCDC 969128 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* [www.ccdc.cam.ac.uk/data request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).

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