

Full Paper

## Novel Reaction of *N,N'*-Bisarylmethanediamines with Formaldehyde. Synthesis of Some New 1,3,5-Triaryl-1,3,5-hexahydrotriazines

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**Abstract:** The acid-catalyzed cyclocondensation of *N,N'*-bisaryl (aryl = 2-pyrimidinyl, 2-pyrazinyl and 4-nitrophenyl) methanediamines **5a-c** with aqueous formaldehyde in refluxing acetonitrile leads to the formation of the corresponding 1,3,5-triaryl-1,3,5-hexahydrotriazines **6a-c**. The stoichiometric reactions of 2-aminopyrimidine and 2-aminopyrazine with aqueous formaldehyde in acetonitrile under reflux conditions also afforded **6a** and **6b**, respectively. Treatment of 2-aminopyrimidine with aqueous formaldehyde in a 3:2 ratio yielded *N,N',N''*-tris(2-pyrimidinyl)dimethylenetriamine (**7a**) as a sole product, which upon subsequent reaction with formaldehyde also afforded **6a**. The reaction of *N,N'*-biphenylmethanediamine with formaldehyde was also investigated.

**Keywords:** *N,N'*-Bisarylmethanediamines, dimethylenetriamine, 1,3,5-hexahydrotriazines.

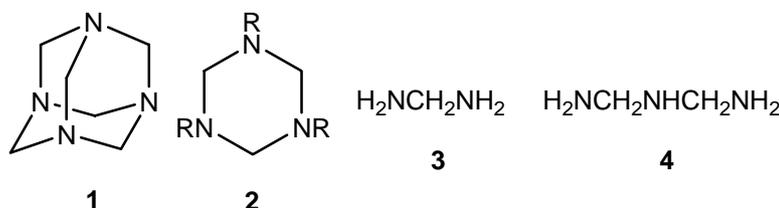
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### Introduction

The reactions of amines and aldehydes (especially formaldehyde) have been the subject of several publications [1-8]. However, there are still unanswered questions about the reaction mechanism(s) and the nature of the products. The best specific example of this type is the reaction between ammonia and formaldehyde leading to the formation of hexamine (**1**). Based on chemical and spectroscopic evidence, Nielsen and Richmond concluded that 1,3,5-hexahydrotriazine (R = H, **2**) is a reaction intermediate

[9,10]. They also suggested the intermediacy of methylenediamine (**3**) and dimethylene-triamine (**4**) in the reaction course (Figure 1). We are not aware, however, of any direct evidence that has been reported for the existence of such intermediates.

**Figure 1.** Structures of hexamine (**1**), 1,3,5-hexahydrotriazine (**2**), methylenediamine (**3**) and dimethylenetriamine (**4**).



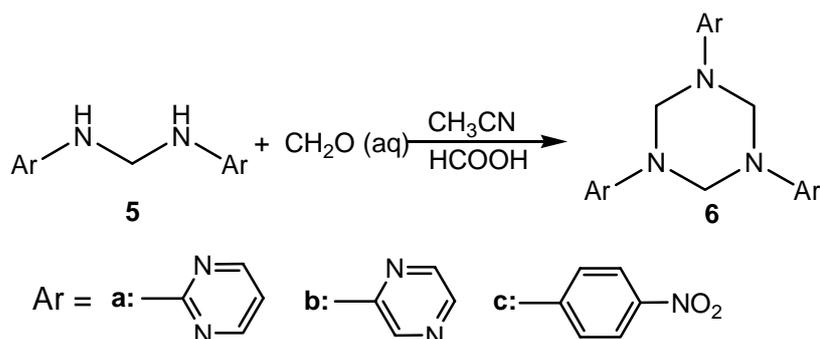
On the other hand, numerous accounts of the synthesis of 1,3,5-trisubstituted 1,3,5-hexahydrotriazines from amines and formaldehyde can be found in the literature. 1,3,5-Hexahydrotriazines are important building blocks in high-explosive compounds [11].

In the present work, the reactions of some *N,N'*-bisarylmethylenediamines **5a-c** as well as arylamines with aqueous formaldehyde were found to produce the corresponding 1,3,5-triaryl-1,3,5-hexahydrotriazines **6a-c** under reflux conditions. In the case of 2-aminopyrimidine, by changing the ratio of amine to formaldehyde, we could isolate the corresponding dimethylenetriamine **7a**, which upon subsequent reaction with another molecule of formaldehyde, led to the formation of 1,3,5-tris(2-pyrimidinyl)-1,3,5-hexahydrotriazine (**6a**). The latter procedure may be considered as an alternative synthetic route to **6a**.

## Results and Discussion

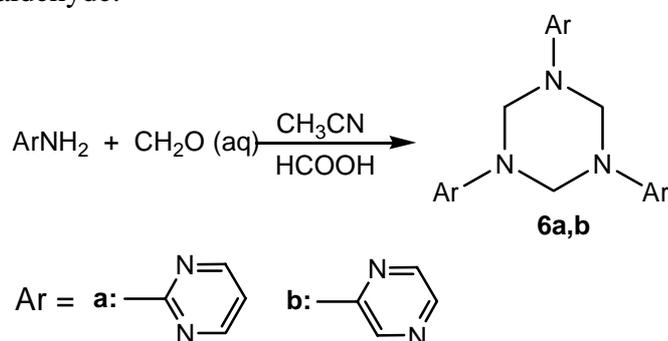
*N,N'*-Bisarylmethylenediamines are easily prepared through the reaction of primary arylamines with formaldehyde at room temperature [12-15]. In the presence of formic acid, the *N,N'*-bisarylmethylene-diamines **5a-c** underwent a smooth reaction with aqueous formaldehyde in refluxing acetonitrile to produce 1,3,5-triaryl-1,3,5-hexahydrotriazines **6a-c** in good yields (Scheme 1). A synthesis of **6c** has already been described in the literature [16].

**Scheme 1.** Formic acid catalyzed reaction of *N,N'*-bisarylmethylenediamines **5a-c** with aqueous formaldehyde.



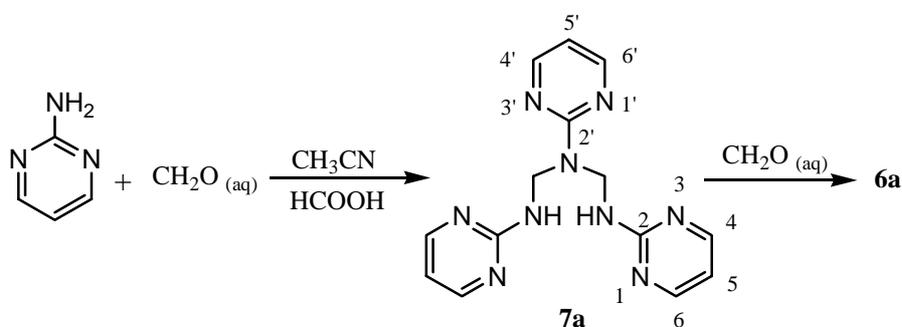
Triazines **6a-c** are stable materials and can be stored at room temperature for extended periods. Their structures were determined from their elemental analysis, MS, IR and high-field  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR spectra. For example, the mass spectrum of **6a** displayed a weak but distinct peak at 321 m/z for the molecular ion. The IR spectrum lacks both amine and carbonyl absorptions. Its  $^1\text{H}$ -NMR spectrum exhibited a sharp singlet at  $\delta = 5.77$  ppm, arising from the methylene protons. The remaining protons of the molecule showed a well-resolved  $\text{AB}_2$  pattern corresponding to the aromatic moieties. It also gave a correct elemental analysis for  $\text{C}_{15}\text{H}_{15}\text{N}_9$ . The proton decoupled  $^{13}\text{C}$ -NMR spectrum showed four distinct resonances, also in agreement with the proposed structure. Finally, the structure of **6a** was further confirmed by synthesis via an alternate route (*vide infra*). The  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR spectra of compounds **6b** and **6c** were similar to those of **6a**.

**Scheme 2.** Reactions of 2-aminopyrimidine and 2-aminopyrazine with aqueous formaldehyde.



The stoichiometric reaction of 2-aminopyrimidine and 2-aminopyrazine with aqueous formaldehyde in refluxing acetonitrile also afforded compounds **6a** and **6b** respectively (Scheme 2). On the other hand, *N,N,N'*-tris(2-pyrimidinyl)dimethylenetriamine (**7a**) was the sole product formed when 2-aminopyrimidine was reacted with formaldehyde in a 3:2 molar ratio. Its subsequent reaction with additional formaldehyde gave **6a** in 82% yield (Scheme 3). This pathway can be viewed as an alternative synthesis of **6a** (*vide supra*).

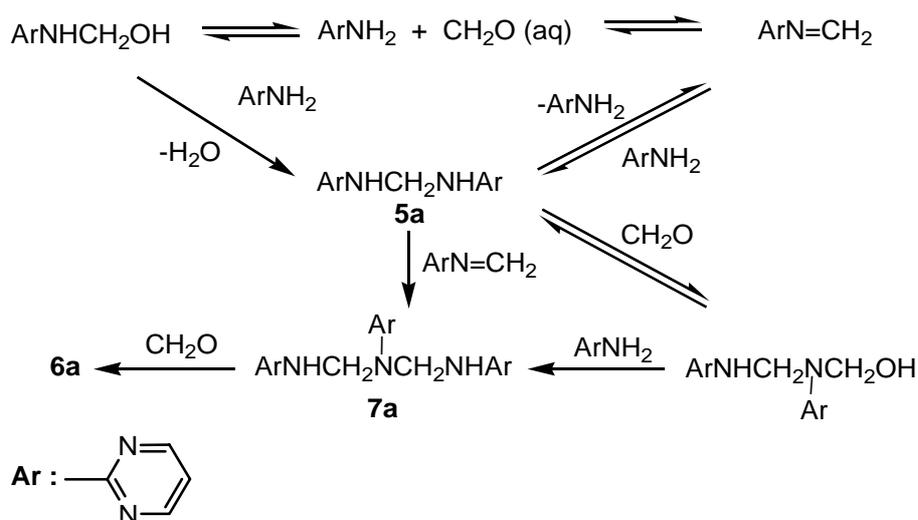
**Scheme 3.** Synthesis of *N,N,N'*-tris(2-pyrimidinyl)dimethylenetriamine (**7a**) and **6a**.



The  $^1\text{H}$ -NMR spectrum of compound **7a** showed a doublet localized at  $\delta = 5.31$  ppm for the methylene groups. The NH protons appeared as a wide triplet at  $\delta = 7.31$  ppm. Upon addition of  $\text{D}_2\text{O}$  to the NMR samples, the NH signal disappeared and the methylene proton signal collapsed to a singlet.

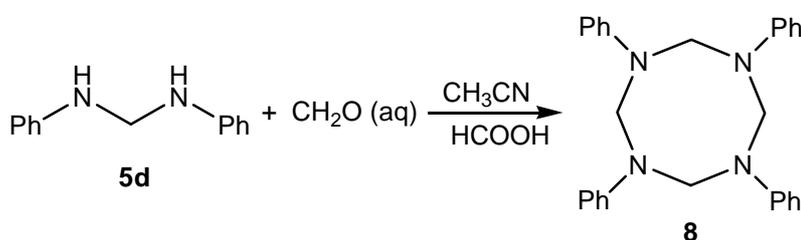
The pyrimidinyl moieties appeared as two well-resolved AB<sub>2</sub> spin systems at 6.65, 8.32 and 6.77, 8.44 ppm. With compound **7a** in hand, we were able to follow the reaction of **5a** with formaldehyde (Scheme 2) by periodically withdrawing reaction samples and comparing the R<sub>f</sub> values of the products with that of **7a** using thin-layer chromatography (TLC). The implication of **7a** as an intermediate in this reaction was confirmed by its appearance and disappearance on the TLC plate. Based on the above-mentioned observations, our proposed mechanism for the formation of **6a** from aqueous formaldehyde and 2-aminopyrimidine is depicted in Scheme 4.

**Scheme 4.** Proposed mechanism for the formation of **6a**.

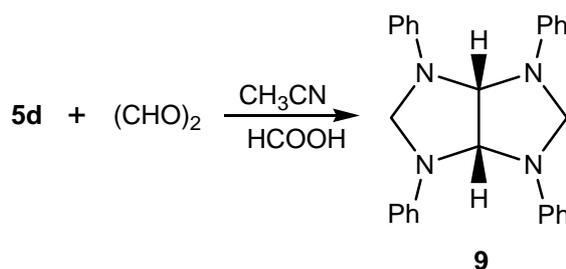


The acid-catalyzed reaction of *N,N'*-bisphenylmethanediamine (**5d**) with aqueous formaldehyde was also carried out in refluxing acetonitrile as well as at room temperature. Surprisingly, in both cases, 1,3,5,7-tetraphenyltetrazocine (**8**, m.p. 298-300 °C decomp.) was quickly formed in high yield (Scheme 5). Randaccio and co-workers had already reported the synthesis of **8** through the reaction of aniline and paraformaldehyde in toluene under reflux conditions [2].

**Scheme 5.** Reaction of *N,N'*-bisphenylmethanediamine (**5d**) with aqueous formaldehyde.



With the exception of aqueous glyoxal, which produced 2,4,6,8-tetraphenyl-2,4,6,8-tetraaza-bicyclo[3.3.0]octane (**9**) upon reaction with **5d**, other aldehydes such as benzaldehyde, acetaldehyde, chloral and propionaldehyde all failed to produce any recognizable products (Scheme 6). Synthesis of compound **9** via the reaction of aniline with glyoxal and formaldehyde has previously been reported [17]. It seems likely that **5d** may be implicated as an intermediate in the reaction.

**Scheme 6.** Reaction of *N,N'*-biphenylmethanediamine (**5d**) with aqueous glyoxal.

## Conclusions

We have found that the reactions of aqueous formaldehyde with *N,N'*-bisarylmethylenediamines having electron withdrawing groups on the aromatic rings leads to the formation of 1,3,5-triaryl-1,3,5-hexahydrotriazines.

## Experimental

### General

All commercially available chemicals and reagents were used without further purification. Melting points were determined with an Electrothermal model 9100 apparatus and are uncorrected. IR spectra were recorded on a Shimadzu 4300 spectrophotometer. The  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR spectra were recorded in  $\text{DMSO-}d_6$  on a Bruker DRX-500 AVANCE spectrometer (operating at 500 MHz for  $^1\text{H}$  and 125.77 MHz for  $^{13}\text{C}$ , respectively), except for the  $^1\text{H}$ -NMR spectra of compounds **8** and **9**, which were recorded on an 80 MHz Bruker AC-80 instrument. Chemical shifts ( $\delta$ ) are reported in ppm and are referenced to the NMR solvent peak. Mass spectra of the products were obtained with a HP (Agilent Technologies) 5937 Mass Selective Detector. Elemental analyses were carried out with a Thermo Finnigan (FLASH 1112 SERIES EA) CHNS-O analyzer. Progress of the reactions was monitored by TLC using precoated aluminium sheets silica gel Merck 60 F<sub>254</sub>.

### General procedures for the synthesis of 1,3,5-triaryl-1,3,5-hexahydrotriazines **6a-c**

#### Procedure A

A stirring solution of *N,N'*-bisarylmethylenediamine (**5a-c**, 1 mmol), 37% aqueous formaldehyde (0.08 g, 1 mmol) and 98% aqueous formic acid (0.01 g, 0.22 mmol) in acetonitrile (20 mL) was refluxed for 20 hours. The resulting solution was then cooled to 0–5 °C and the solid formed was filtered off, washed with cold acetonitrile and dried.

*1,3,5-Tris(2-pyrimidinyl)-1,3,5-hexahydrotriazine (6a)*: White crystals (70%); m.p. 228–230 °C (from acetonitrile); IR (KBr): 3058, 2902, 1587, 1483, 1352, 1263, 960  $\text{cm}^{-1}$ ;  $^1\text{H}$ -NMR  $\delta$ : 5.81 (s, 6H,  $\text{CH}_2$ ), 6.79 (t, 3H,  $J = 4.7$  Hz, pyrimidine H-5), 8.47 (d, 6H,  $J = 4.7$  Hz, pyrimidine H-4, H-6);  $^{13}\text{C}$ -NMR  $\delta$ : 57.17, 111.79, 158.30, 161.30 ppm; MS (EI)  $m/z$ : 321 ( $\text{M}^+$ ); Anal. Calcd. for  $\text{C}_{15}\text{H}_{15}\text{N}_9$ : C, 56.07; H, 4.67; N, 39.25; Found: C, 55.96; H, 4.69; N, 39.40.

*1,3,5-Tris(2-pyrazinyl)-1,3,5-hexahydrotriazine (6b)*: White crystals (79%); m.p. 196-198 °C (from acetonitrile); IR (KBr): 3085, 2912, 1579, 1523, 1317, 1257, 1130, 997 cm<sup>-1</sup>; <sup>1</sup>H-NMR δ: 5.72 (s, 6H, CH<sub>2</sub>), 7.88 (d, 3H, *J* = 2.5 Hz, pyrazine H-5), 8.06 (dd, 3H, *J* = 2.5, 1.1 Hz, pyrazine H-6), 8.62 (d, 3H, *J* = 1.1 Hz, pyrazine H-3); <sup>13</sup>C-NMR δ: 59.58, 133.81, 135.06, 142.05, 153.95 ppm; MS (EI) *m/z*: 321 (M<sup>+</sup>); Anal. Calcd. for C<sub>15</sub>H<sub>15</sub>N<sub>9</sub>: C, 56.07; H, 4.67; N, 39.25; Found: C, 55.90; H, 4.70; N, 39.01.

*1,3,5-Tris(4-nitrophenyl)-1,3,5-hexahydrotriazine (6c)*: Yellow crystals (62%); m.p. 285-287 °C (from 1:1 DMSO-EtOH, lit. [16] 286-287 °C); IR (KBr): 3076, 2906, 1589, 1490, 1390, 1311, 1230 cm<sup>-1</sup>; <sup>1</sup>H-NMR δ: 5.35 (s, 6H, CH<sub>2</sub>), 7.23 and 8.10 (AA'BB', 12H, ArH); <sup>13</sup>C-NMR δ: 63.64, 115.39, 126.41, 139.89, 153.23 ppm; MS (EI) *m/z*: 450 (M<sup>+</sup>); Anal. Calcd. for C<sub>21</sub>H<sub>18</sub>N<sub>6</sub>O<sub>6</sub>: C, 56.00; H, 4.00; N, 18.66; Found: C, 55.86; H, 3.95; N, 18.83.

### Procedure B

A stirring solution of 2-aminopyrimidine (or 2-aminopyrazine) (0.19 g, 2 mmol), 37% aqueous formaldehyde (0.16 g, 2 mmol) and 98% aqueous formic acid (0.02 g, 0.22 mmol) in acetonitrile (10 mL) was refluxed for 20 hours. The reaction mixture was then cooled to 0-5 °C and the solid formed was filtered off, washed with cold acetonitrile and dried. Recrystallization from acetonitrile gave pure crystals of **6a** (or **6b**) in 83% (87%) yield, which had identical melting points and IR and NMR spectra with the products obtained using *Procedure A*

### *N,N',N''-Tris(2-pyrimidinyl)dimethylenetriamine (7a)*

A stirring solution of 2-aminopyrimidine (0.3 g, 3.15 mmol), 37% aqueous formaldehyde (0.16 g, 2 mmol) and 98% aqueous formic acid (0.02 g, 0.44 mmol) in acetonitrile (10 mL) was refluxed for 15 hours. The reaction mixture was then cooled to 0-5 °C and the solid formed was filtered off, washed with cold acetonitrile and dried. Recrystallization from 1:1 DMSO-H<sub>2</sub>O gave white pure crystals of **7a** (75%); m.p. 218-220 °C; IR (KBr): 3238 (N-H), 3103, 2979, 1596, 1541, 1460, 1377, 1164 cm<sup>-1</sup>; <sup>1</sup>H-NMR δ: 5.31 (d, 4H, *J* = 6.1 Hz, CH<sub>2</sub>), 6.65 (t, 2H, *J* = 4.7 Hz, pyrimidine H-5), 6.77 (t, 1H, *J* = 4.7 Hz, pyrimidine H-5'), 7.35 (t, 2H, *J* = 6.1 Hz, NH), 8.32 (d, 4H, *J* = 4.7 Hz, pyrimidine H-4, H-6), 8.44 (d, 2H, *J* = 4.7 Hz, pyrimidine H-4', H-6'); <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub> + D<sub>2</sub>O) δ: 5.29 (s, 4H, CH<sub>2</sub>), 6.65 (t, 2H, *J* = 4.8 Hz, pyrimidine H-5), 6.76 (t, 1H, *J* = 4.4 Hz, pyrimidine H-5'), 8.30 (d, 4H, *J* = 4.8 Hz, pyrimidine H-4, H-6), 8.43 (d, 2H, *J* = 4.4 Hz, pyrimidine H-4', H-6'); <sup>13</sup>C-NMR δ: 55.36, 111.97, 112.22, 158.66, 158.79, 162.04, 62.88 ppm; MS (EI) *m/z*: 309 (M<sup>+</sup>, not seen), 201, 108 (base peak), 96; Anal. Calcd. for C<sub>14</sub>H<sub>15</sub>N<sub>9</sub>: C, 54.36; H, 4.85; N, 40.77; Found: C, 54.37; H, 4.91; N, 40.91.

### Reaction of **7a** with aqueous formaldehyde

A stirring solution of **7a** (0.31 g, 1 mmol) 37% aqueous formaldehyde (0.08 g, 1 mmol) and 98% aqueous formic acid (0.01 g, 0.22 mmol) in a mixture of acetonitrile (20 mL) and DMF (20 mL) was refluxed for 20 hours. Water (50 mL) was added to the resulting solution and the white solid formed

was filtered off and dried. Recrystallization from acetonitrile gave white pure crystals (82%), identical with **6a** based on melting point and NMR data.

#### *1,3,5,7-Tetraphenyltetrazocine (8)*

A solution of *N,N'*-bisphenylmethanediamine (**5d**, 0.2 g, 1 mmol), 37% aqueous formaldehyde (0.08 g, 1 mmol) and 98% aqueous formic acid (0.01 g, 0.22 mmol) in acetonitrile (2 mL) was stirred at room temperature for 2 hours. The white solid formed was then filtered off, washed with cold acetonitrile and dried. Recrystallization from DMSO gave white crystals of **8** (85%), m.p. 298-300 °C (lit. [2] 303 °C); IR (KBr): 3026, 2916, 1596, 1502, 1371, 1261, 1164 cm<sup>-1</sup>; <sup>1</sup>H-NMR δ: 4.88 (s, 8H, CH<sub>2</sub>), 6.97-7.17 (m, 20H, ArH); MS (EI) m/z: 420 (M<sup>+</sup>); Anal. Calcd. for C<sub>28</sub>H<sub>28</sub>N<sub>4</sub>: C, 80.00; H, 6.66; N, 13.33; Found: C, 79.82; H, 6.69; N, 13.52.

#### *2,4,6,8-Tetraphenyl-2,4,6,8-tetraazabicyclo[3.3.0]octane (9)*

A solution of *N,N'*-bisphenylmethanediamine (**5d**, 0.4 g, 2 mmol), glyoxal (40% aqueous solution, 0.14 g, 1 mmol) and formic acid (98% aqueous solution, 0.01 g, 0.22 mmol) in acetonitrile (4 mL) was stirred at room temperature for 5 hours. The white solid formed was then filtered, washed with cold acetonitrile and dried. Recrystallization from acetonitrile gave white crystals of **9** (78%); m.p. 209-210 °C (lit. [17] 210-211 °C); IR (KBr): 3030, 2980, 1595, 1492, 1325 cm<sup>-1</sup>; <sup>1</sup>H-NMR δ: 4.63 and 4.82 (ABq, 4H, *J* = 7.4 Hz, CH<sub>2</sub>), 6.39 (s, 2H, CH), 6.75-7.27 (m, 20H, ArH); Anal. Calcd. for C<sub>28</sub>H<sub>26</sub>N<sub>4</sub>: C, 80.38; H, 6.22; N, 13.39; Found: C, 80.17; H, 6.14; N, 13.55.

### Acknowledgements

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*Sample Availability:* Samples of compounds **6a**, **6b** and **7a** are available from authors.