1,2-DIHYDRO-1,3,5-TRIAZINES FROM 1,3-DIAZA-1,3-BUTADIENES

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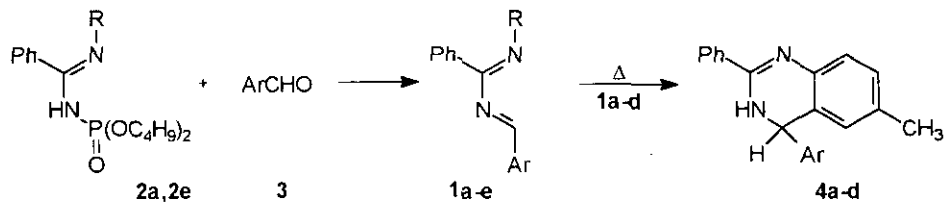
Abstract - The 4-aryl-1-(4-methylphenyl)-2-phenyl- and 1-benzyl-2,4-diphenyl-1,3-diaza-1,3-butadienes are nearly quantitatively transformed into the corresponding 1,3,5-triazines when allowed to stand at room temperature in benzene solution. The mechanism of the reaction is discussed.

Recently[1,2] we reported the synthesis of 1,3-diazabuta-1,3-dienes (**1a-e**) starting from phosphoramidates (**2a,e**) and aromatic aldehydes (**3**). Diazadienes (**1a-d**) undergo thermal 6π electrocyclic ring closure to give 3,4-dihydroquinazolines (**4**).[1,3] Thus, these reactions are strictly thermal induced (refluxing toluene or xylene) and when 1,3-diaza-1,3-dienes (**1a-d**) were allowed to stand at room temperature in benzene solution a different reaction took place and 1,2-dihydro-1,3,5-triazines (**5a-d**) (73-97%) and aldimines (52-67%) (**6a-d**) were isolated after chromatographic purification over silica gel. The same behaviour was observed for diazadiene (**1e**), which structure is incompatible with an electrocyclic reaction, Scheme 1.



1-6	R	Ar
a	CH_3	
b	CH_3	Cl
c	CH_3	NO_2
d	CH_3	OCH_3
e	CH_2	

Scheme 1

Compounds (**5a-e**) originate formally from two molecules of azadiene and the substitution pattern around triazine ring was clearly established for triazines (**5b**) and (**5e**) through 2D NOESY experiments and

extended by analogy to the entire series. Diagnostic NOE interactions for compounds (**5b**) and (**5e**) are reported in Figure 1.

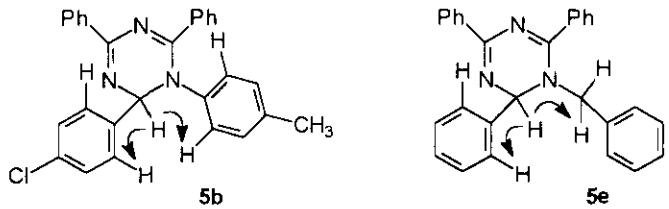
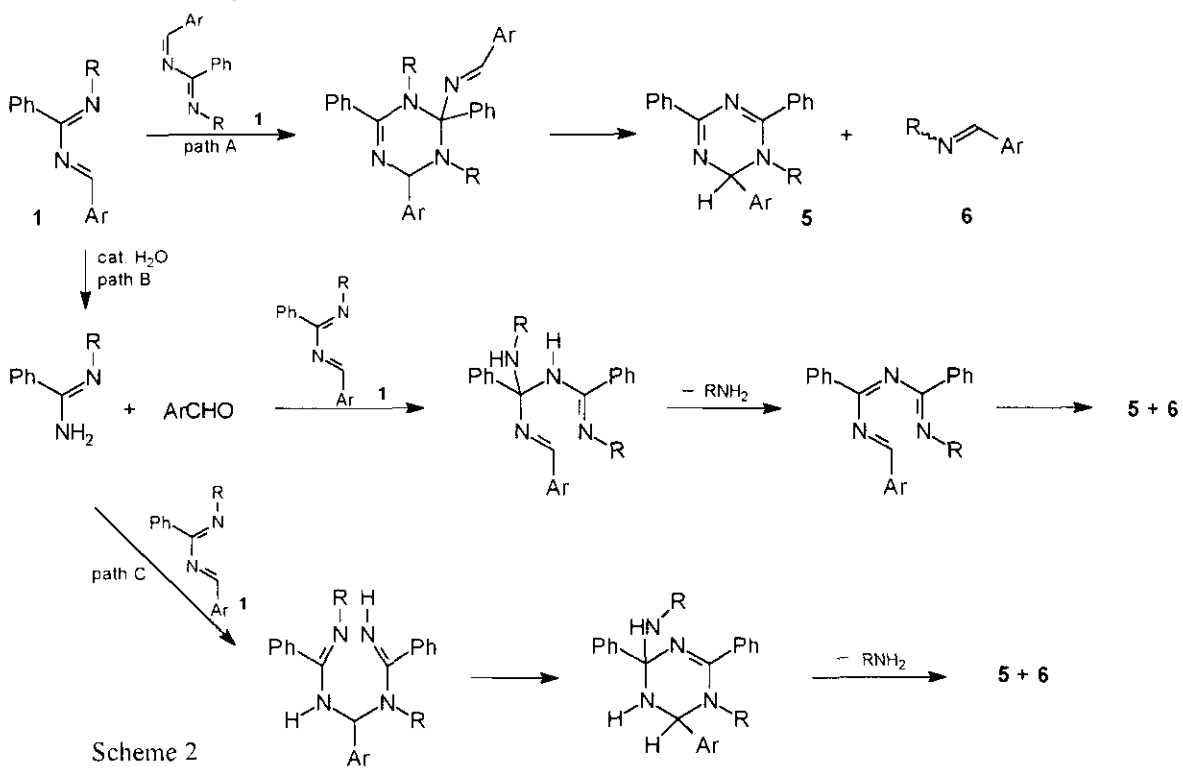


Figure 1

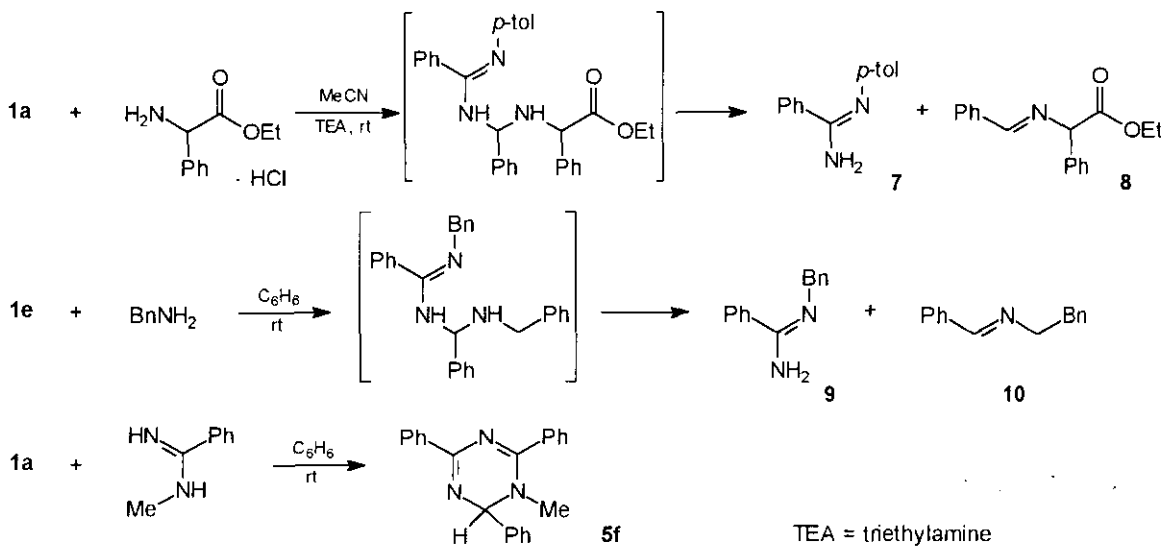
The 1,3-diaza-1,3-dienes have been proposed as intermediates, in the 1,2-dihydro-1,3,5-triazine ring formation, in the reactions involving the condensation of an aryl aldehyde with benzamidine[4] or with *N*-benzylbenzamidine[5] and in the thermolysis of *N*-benzyl-substituted amidrazone ylides[6] and two different mechanism have been proposed, Scheme 2. Following path A[4] the reaction involves a [4+2] cycloaddition reaction between two molecules of diene (**1**) followed by cleavage of two vicinal carbon-nitrogen bonds to give triazine (**5**) and benzaldimine (**6**). Instead in path B[5,6] the presence of a catalytic amount of water promotes the partial hydrolysis of diazadiene (**1**) to the corresponding benzamidine and arylaldehyde. Subsequent nucleophilic attack of the unsubstituted nitrogen of benzamidine on C2 of the diene followed by amine elimination and cyclization give the final product (**5**). Water is restored in the condensation between the aryl aldehyde and the primary amine. Moreover, as discussed by Weis,[7] the formation of the triazine ring *via* cyclization of a geminal diamidine generated by nucleophilyc attack on C4 of diene system cannot be excluded, path C, Scheme 2.



Scheme 2

However, in the second step of path A, the formation of the final product by cleavage of two vicinal C-N bonds is, in our opinion, unlikely. Moreover we tested the capability of diazadienes (**1**) to react in cycloaddition reactions with electron rich dienophiles such enol ethers and enamines and the 1,2-dihydro-1,3,5-triazines (**5a**, **5c** and **5e**) were the sole isolable products when the corresponding diazadienes (**1a**, **1c** and **1e**) reacted, in benzene solution at room temperature, with ethyl vinyl ether or with 1-morpholino-cyclopentene.

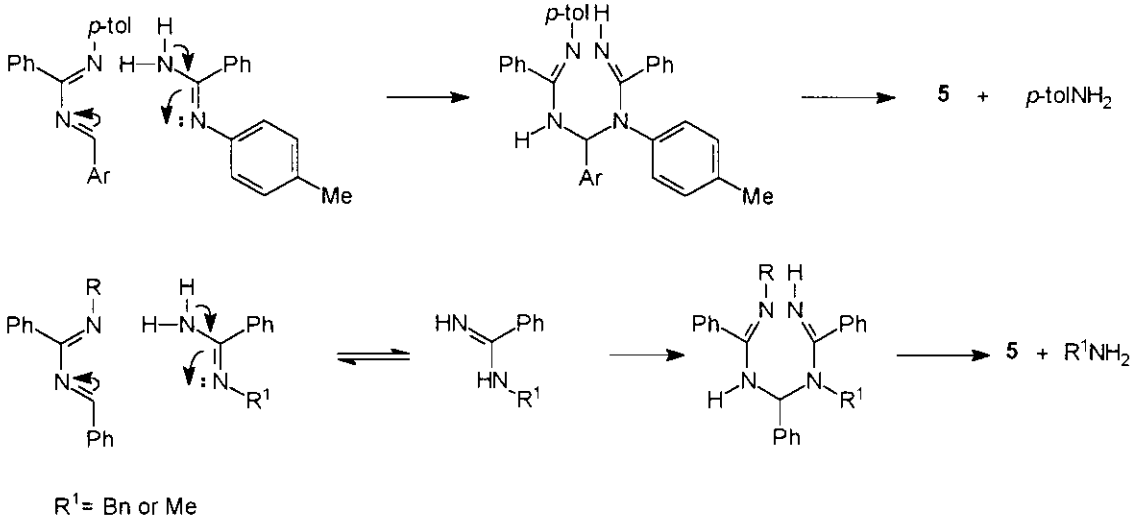
Instead diazadienes (**1a**) and (**1e**) react with simple nucleophiles such L(+)-phenylglycine ethyl ester or benzylamine yielding, through an amidineaminal intermediate generated by addition of the nucleophile over N3-C4 double bond, the *N*-*p*-tolylbenzamidine (**7**) and the benzylideneaminophenylacetic acid ethyl ester (**8**) or respectively, the *N*-benzylbenzamidine (**9**) and the *N*-benzylbenzaldimine (**10**). Moreover when diazadiene (**1a**) reacted with *N*-methylbenzamidine it was possible to isolate, beside small quantities of triazine (**5a**) and benzaldimine (**6a**), the 1-methyl-2,4,6-triphenyl-1,2-dihydro-1,3,5-triazine (**5f**), Scheme 3. Also for **5f** the substitution pattern around triazine ring was demonstrated by 2D NOESY experiment.



Scheme 3

Taking into account these results we can reasonably postulate that **5f**, as well as **5a-e**, was formed through the mechanism described in Scheme 2, path C which involves nucleophilyc attack of the *N*-substituted nitrogen atom of benzamidine over C4 carbon atom of the diene system, giving rise to a diamidine which by ring closure and *p*-tolylamine elimination gave the final product. The good nucleophilic character of amidines is related to the high electron density of imine residue and to the bifunctional nature of the nucleophile which can concertedly attack the N3-C4 double bond forming a tetrahedral intermediate without creation of zwitter ions.[8] It is worth to note that the reaction showed complete regioselectivity in both reagents and this is in agreement with the electronic structure of the 1,3-diaza-1,3-dienes which

chemistry is characterised by pronounced charge alternation.[9] However, although many examples of nucleophilic reactions involving the amidine system with a wide variety of electrophiles are present in the literature, only few of these involve monosubstituted amidines[10] and the related problems of regioselectivity, connected with imine-amine tautomerism present in these latter compounds, are not treated. In our case, regioselectivity was observed for both *N*-tolyl and *N*-alkyl (benzyl or methyl) substituted benzamidines and this can be attributed to the prevalence of the imino tautomer in *N*-tolylbenzamidine and to the influence of the electron donating alkyl substituent in the *N*-benzyl and *N*-methylbenzamidine which favors the attack of the substituted nitrogen even if alkylbenzamidines can exist in equilibrium between the imino and amino tautomers, Scheme 4.[11]



Scheme 4

EXPERIMENTAL

Merck silica gel 60 F_{254} thin-layer plates were employed for thin layer chromatography. Merck silica gel (70-120 mesh) was employed for column chromatography. Merck silica gel (230-400 mesh) was employed for flash column chromatography. Melting points, measured with a Büchi apparatus, are "uncorrected". IR spectra were recorded on a FT-IR Perkin Elmer 16 PC spectrophotometer, using KBr tablets. ^{1}H-NMR (200 MHz) and ^{13}C-NMR (50.3 MHz) spectra were recorded in $CDCl_3$, with a Varian-Gemini 200 spectrometer. EI (70eV) MS spectra were recorded with a TSQ 700 Finnigan/Mat instrument. 1,3-Diaza-1,3-butadiene (**1a-d**),[1] (**1e**)[2] and *N*-methylbenzamidine[12] are known compounds and were prepared according to described methods. All chemicals and solvents are commercially available and were used after distillation or treatment with drying agents.

1,2-Dihydro-1,3,5-triazines (5a-e) and aldimines (6a-e). A solution of the appropriate 1,3-diaza-1,3-butadienes (**1a-e**) (1.5 mmol) in benzene (5 mL) was allowed to stand at room temperature until no more starting compound was detectable by TLC. The reaction mixture was evaporated to dryness and the residue was chromatographed over a silica gel column (ratio crude/silica gel, 1:40). Elution with suitable solvent **yielded** progressively the aldimine (**6a-e**), which were identified by analysis of ^{1}H-NMR and IR spectra, and triazines (**5a-e**).

5a: purified by chromatography (petroleum ether/triethylamine 9:1); white solid; mp 140-142 °C (*i*-Pr_2O); yield 82%; ^{1}H-NMR ($CDCl_3$) δ 2.25 (s, 3H); 6.35 (s, 1H); 6.87 and 6.98 (AA'BB' system, 4H, J = 8); 7.26-7.48 (m, 9H); 7.70 (m, 2H); 7.78 (m, 2H); 8.38 (m, 2H). EI MS *m/z* (relative intensity) 401 (M^+, 46); 400 (16); 324(40); 297 (26); 194 (100), 180 (50), 148 (44), 118 (40); 91 (92). Anal. Calcd for $C_{28}H_{23}N_3$: C, 83.76; H, 5.77; N, 10.47. Found: C, 83.72; H, 5.74; N, 10.42.

5b: purified by chromatography (petroleum ether/triethylamine 9:1); pale yellow solid; mp 72-75 °C (*i*-Pr_2O); yield 73%; ^{1}H-NMR ($CDCl_3$) δ 2.25 (s, 3H); 6.32 (s, 1H); 6.84 and 6.96 (AA'BB' system, 4H, J = 8); 7.34 and 7.62 (AA'BB' system, 4H, J = 8.4); 7.24-7.46 (m, 6H); 7.73 (m, 2H); 8.34 (m, 2H). Anal. Calcd for $C_{28}H_{22}ClN_3$: C, 77.14; H, 5.09; N, 9.64. Found: C, 77.06; H, 5.02; N, 9.58.

5c: purified by chromatography (cyclohexane/EtOAc 95:5); yellow solid; mp 206-209 °C (*i*-Pr_2O); yield 88%; ^{1}H-NMR ($CDCl_3$) δ 2.28 (s, 3H); 6.46 (s, 1H); 6.85 and 7.01 (AA'BB' system, 4H, J = 8); 7.21-7.52 (m, 6H); 7.81 (m, 2H); 7.89 and 8.26 (AA'BB' system, 4H, J = 9); 8.37 (m, 2H). Anal. Calcd for $C_{28}H_{22}N_4O_2$: C, 75.32; H, 4.97; N, 12.55. Found: C, 75.28; H, 4.95; N, 12.52.

5d: purified by chromatography (petroleum ether/triethylamine 9:1); white solid; mp 155-157 °C (*i*-Pr_2O); yield 75%; ^{1}H-NMR ($CDCl_3$) δ 2.27 (s, 3H); 3.82 (s, 3H); 6.30 (s, 1H); 6.86 and 6.97 (AA'BB' system, 4H, J = 8); 7.32 and 7.61 (AA'BB' system, 4H, J = 9); 7.35-7.48 (m, 6H); 7.75 (m, 2H); 8.37 (m, 2H). Anal. Calcd for $C_{29}H_{25}N_3O$: C, 80.72; H, 5.84; N, 9.74. Found: C, 80.68; H, 5.81; N, 9.70.

5e[5]**:** purified by chromatography (cyclohexane/TEA 9:1); white solid; mp 140-143 °C (*i*-Pr_2O); yield 97%; ^{1}H-NMR ($CDCl_3$) δ 4.15 and 5.00 (AB quartet, 2H, J = 14); 6.00 (s, 1H); 7.45 (m, 14H); 7.72 (m, 4H); 8.40 (m, 2H). Anal. Calcd for $C_{28}H_{23}N_3$: C, 83.76; H, 5.77; N, 10.47. Found: C, 83.68; H, 5.72; N, 10.45.

Reaction of 1a with L(+)-phenylglycine ethyl ester. To a solution of 1,3-diaza-1,3-butadiene (**1a**) (0.45 g, 1.5 mmol) in dry acetonitrile (10 mL) L(+)-phenylglycine ethyl ester hydrochloride (0.32 g, 1.5 mmol) and triethylamine (0.61 g, 0.83 mL, 6 mmol) were added. The reaction mixture was allowed to stand at rt until no more starting compound was detectable by TLC (2 h) then evaporated to dryness and the residue, washed with saturated $NaHCO_3$, was extracted twice with ethyl acetate. The organic layer dried over

anhydrous sodium sulfate was evaporated under reduced pressure and the residue was purified by flash chromatography. Elution with petroleum ether/triethylamine (9:1) yielded progressively the benzylideneaminophenylacetic acid ethyl ester (**8**) (0.24 g, 75%) and the *N*-*p*-tolylbenzamidine (**7**) (0.33 g, 81%) which was identified by comparison (^{1}H-NMR, IR) with an authentic sample.[13]

8[14]: white solid, mp 60-62 °C (petroleum ether); ^{1}H-NMR ($CDCl_3$) δ 1.25 (t, 3H, J = 7); 4.22 (m, 2H); 5.21 (s, 1H); 7.32-7.57 (m, 8H); 7.85 (m, 2H); 8.36 (s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 14.6, 61.8, 77.1, 128.4, 128.5, 129.0, 129.1, 129.2, 131.7, 136.3, 138.8, 164.1, 171.5. IR (cm^{-1}): 1732 (C=O), 1637 (C=N).

Reaction of 1e with benzylamine. A solution of 1,3-diaza-1,3-butadiene (**1e**) (0.45 g, 1.5 mmol) and benzylamine (0.32 g, 0.33 mL, 3 mmol) in dry benzene (10 mL) was allowed to stand at rt until no more starting compound was detectable by TLC (4 h). The reaction mixture was evaporated to dryness and the crude material was chromatographed over a silica gel column (ratio crude/silica gel, 1:40). Elution with petroleum ether/triethylamine (8:2) yielded progressively the aldimine (**10**) and *N*-benzylbenzamidine (**9**), which were identified by comparison (^{1}H-NMR, IR) with authentic samples.

Reaction of 1a with *N*-methylbenzamidine. A solution of 1,3-diaza-1,3-butadiene (**1a**) (0.45 g, 1.5 mmol) and *N*-methylbenzamidine (0.20 g, 1.5 mmol) in dry benzene (7 mL) was allowed to stand at rt until no more starting compound was detectable by TLC (4 days). The reaction mixture was evaporated to dryness and the residue was chromatographed over a silica gel column (ratio crude/silica gel, 1:40). Elution with petroleum ether/triethylamine (8:2) yielded the 1-methyl-2,4,6-triphenyl-1,2-dihydro-1,3,5-triazine (**5f**) (0.32 g, 65%).

5f[6]: white solid, mp 162-165 °C (*i*-Pr_2O); ^{1}H-NMR ($CDCl_3$) δ 3.05 (s, 3H); 6.05 (s,1H); 7.35-7.65 (m, 13H); 8.30 (m, 2H). Anal. Calcd for $C_{22}H_{19}N_3$: C, 81.20; H, 5.89; N, 12.91. Found: C, 81.17; H, 5.87; N, 12.86.

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