SELECTIVE REACTIONS WITH 3-CHLORO-5,6-DIPHENYL 1,2,4-TRIAZINE.

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ABSTRACT

The results of allowing 3-chloro-5,6-diphenyl-1,2,4-triazine to react with various active methylene compounds, such as, cyanoacetamide, chloroacetamide, malononitrile and cyanoacetic acid hydrazide are discussed. Also, the interaction between 3-chloro-as-triazine with hydrazino derivatives or aldehyde hydrazones was reported. Both reactions conducted neutral or alkaline medium, led to the formation of various heterocyclic systems attached to the as-triazine nucleus at position three.

INTRODUCTION

The relatively easier replacement of the chlorine atom in 3-position of as-triazine nucleus with active methylene compounds as compared to acid hydrazide and hydrazino derivative, is greatly influenced, by the kind of the nucleophile, influence of neighbouring groups, basic or neutral media and reaction conditions.

The U.V., I.R. and P.M.R. spectra of some of these compounds have been presented for characterization.

RESULTS AND DISCUSSION

In continuation of our earlier work on uncondensed 1,2,4-triazine derivatives, the present study deals with the synthesis of
heterocyclic systems containing \((5,6\text{-diphenyl-1,2,4-triazin-3-yl})\) (Zaheer 1979; 1982; 1983; 1984).

The reaction of 3-chloro-as-triazine (I) with cyanoacetamide, chloroacetamide and malononitrile in presence of dry pyridine or D. M.F. resulted in the formation of acetamide derivatives \(\Pi_a\), di-cyanomethane derivative \(\Pi_c\) respectively (Mizuna, 1954). Alkaline hydrolysis of \(\Pi_c\) using ethanolic KOH, gave the malonamide derivative \(\Pi_d\).

\[
\begin{align*}
\text{(I)} & \quad \text{(II)} \\
\begin{array}{ll}
\text{Ph} & \quad \text{Ph} \\
\text{N} & \quad \text{N} \\
\text{Cl} & \quad \text{R} \\
\text{N} & \quad \text{R}'
\end{array}
\end{align*}
\]

\(\begin{array}{ll}
\text{R} & \quad \text{R}' \\
\text{a} & \quad \text{CN} \quad \text{CONH}_2 \\
\text{b} & \quad \text{CL} \quad \text{CONH}_2 \\
\text{c} & \quad \text{CN} \quad \text{CN} \\
\text{d} & \quad \text{CONH}_2 \quad \text{CONH}_2
\end{array}\)

Cyclocondensation of \(\Pi_a\) with glacial acetic acid-sodium acetate yielded pyrimidino (6, 1-b) 1,2,4-triazine derivatives \((\Pi_{a\ b})\), while \(\Pi_d\) under the same condition affords 2-methyl-5 \((5,6\text{-diphenyl-1,2,4-triazin-3-yl})\)-Pyrimidin4,6-dione (IV) (Dornow, 1957).

\[
\begin{align*}
\text{(III)} & \quad \text{(IV)} \\
\begin{array}{ll}
\text{Ph} & \quad \text{Ph} \\
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{O} \\
\text{R} & \quad \text{CH}_3 \\
\text{O} & \quad \text{CH}_3
\end{array}
\end{align*}
\]

\(\begin{array}{ll}
\text{R} & \quad \text{R} \\
\text{a} & \quad \text{CN} \\
\text{b} & \quad \text{Cl}
\end{array}\)
Reduction of II using zinc dust-acetic acid in presence of ethanol, gave the reduction product V, which successfully cyclized in glacial acetic acid-sodium acetate to give 2-methyl-5 (4,5-dihydro 5,6-diphenyl-1,2,4-triazin-3-yl)-6 (2H)-pyrimidin-4-one (IV) (Smagin, 1972; 1974).

![Chemical structures](image)

(V)  

(VI)

Interaction of I with cyanoacetic acid hydrazide in dry pyridine gave the corresponding hydrazide product VII (Mizuno, 1954). To prove the structure of VII, was obtained by condensation with acetone to give the condensation product VIII. Further confirmation of the structure VII, was reported by acidic hydrolysis to give 4 (5,6-diphenyl-1,2,4-triazin-3-yl)-pyrazol-3,5-dione (IX) (Zaher, 1979).

On the other hand, treatment of I with cyanoacetic acid hydrazide in dry benzene-triethylamine, gave N1-cyanomethyl, N2 (5,6-diphenyl-1,2,4-triazin-3-yl) hydrazine (X), which underwent condensation with vanillin in the presence of sodium-ethoxide gave the condensation product (XI), while basic hydrolysis of X yielded 1-(5,6-diphenyl-as-triazin-3-yl) 4 (2H)-pyrazol-3,5-dione (XII) (Scheme 1) (Sasaki, 1969).

The formation of II, VII and X under the reaction condition applied could be a supporting evidence for the comparative chemistry of active methylene compounds and hydrazido derivatives when reacting with 3-chloro-as-triazine (I).
1. Dry pyridine; 2. Acetone, EtOH; 3. Dilute HCl
4. Dry benzene, triethylamine; 5. Vanilin, NaOC₂H₅; 6. 2N NaOH

Scheme 1
Treatment of I with 2-hydrizinobenzimidazole resulted in the formation of hydrazo compound XIII. Heating XIII with 1,2-dibromoethan in alcoholic KOH, affords N\(^1\)(5,6-diphenyl-1,2,4-triazin-3-yl)-1,2,4-triazino (3,4-b) benzimidazole (XIV).

![Chemical structures](image)

(XIII) (XIV)

3-Chloro-as-triazine (I) was allowed to react with aldehyde hydrazino derivatives XV\(_{a-e}\), in dry benzene-triethylamine gives the corresponding alkylidene and aryldene derivatives XVI\(_{a-c}\).

\[
\text{H}_2\text{N-N = CH-R}
\]

(XV) R

a. CCl\(_3\)
b. C\(_6\)H\(_4\)OH (O)
c. C\(_6\)H\(_3\)(OH)\(_2\)(o,p)

(XVI)

Cycloaddition of XVI\(_e\), using mercapto acetic acid in dry benzene gave the thiapyridizinone derivative XVIII (Krishna, 1983). The likely mechanism for this type of reactions may be the 1,3-dipolar cycloaddition to an unequivocal dienophile via the formation of intermediate XVII.
Further, the 3-chloro-as-triazine (I) on reaction with N-acetyl, N-phenyl-hydrazine in dry pyridine gave N¹-phenyl-N²-acetyl, (5,6-diphenyl-1,2,4-triazin-3-yl) hydrazine (XIX).

Finally, the attempted to reduction of I using zinc dustacetic acid in ethanol, led to direct formation of tetrahydro-1,2,4-triazinone derivative (XX). The structure of XX was confirmed from spectral, analytical data and the authentic sample prepared (m.p. & m.m.p) (Piskala, 1964; Pinson, 1972; Polonovski, 1954; 1955).
EXPERIMENTAL

All melting points are uncorrected. The U.V. spectrum of the compounds have been recorded on Perkin-Elmer (Type 550S) UV vis. spectrophotometer using ethanol as the solvent. I. R. spectra of the compounds were taken on KBr disc in Perkin Elmer model 293 spectrophotometer. The P.M.R. spectra were determined with a varian A-60 A instrument.

3- Chloro-5,6-diphenyl-1,2,4-triazine (I) was prepared after the procedure described by P.V. Laakso, et al. (Zaher, 1979).

(5,6-Diphenyl-1,2,4-triazin3-yl) acetamide derivatives (IIa, b):

A mixture of equimolecular amounts of I and cyanoacetamide or chloroacetamide in dry pyridine (20 ml.), was heated under reflux for one hr. The reaction mixture was cooled then acidified (dil HCl) and the solid obtained was crystallized from the proper solvent to give IIa, b respectively (Table 1). I.R. spectrum of IIa shows absorption bands at 3350 & 3180 cm⁻¹(NH) between 2260-2240 cm⁻¹ (C≡N) and at 1650 cm⁻¹(C=O).

3- (Dicyanomethan)-5,6-diphenyl-1,2,4-triazine (IIc):

A suspension of I (0.01 M) in dry pyridine (50 ml.) and malononitrile (0.01 M) was heated under reflux for 2 hr., called and then poured onto HCl-ice. The solid obtained was recrystallized to give IIc(Table 1). I.R. of IIc shows a bands at 2200 cm⁻¹ (C≡N) and 1470 - 1440 cm⁻¹ (CH). U.V. (in ethanol as solvent) λ_max 320 mm.

3-(Malonamide)-5,6-diphenyl-1,2,4-triazine (IId):

Compound IIc(0.01 M) in ethanolic KOH (10 % - 50 ml.) was refluxed for 4 hours, cooled, neutralized and solid precipitated was
filtered. The solid obtained was crystallized from the proper solvent give $\Pi_a$(Table 1).

**TABLE 1**

**PHYSICAL DATA OF THE COMPOUND II-X**

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>M.p. °C</th>
<th>Solvent</th>
<th>Yield %</th>
<th>Mol. Formula</th>
<th>Analysis of Nitrogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Pi_a$</td>
<td>237</td>
<td>CH$_2$CO$_2$H</td>
<td>80</td>
<td>C$<em>{10}$H$</em>{12}$N$_4$O</td>
<td>22.21</td>
</tr>
<tr>
<td>$\Pi_b$</td>
<td>165</td>
<td>C$_6$H$_8$OH</td>
<td>80</td>
<td>C$<em>{10}$H$</em>{12}$N$_4$ClO*</td>
<td>17.23</td>
</tr>
<tr>
<td>$\Pi_c$</td>
<td>220</td>
<td>C$_6$H$_8$</td>
<td>70</td>
<td>C$<em>{10}$H$</em>{12}$N$_4$</td>
<td>23.56</td>
</tr>
<tr>
<td>$\Pi_d$</td>
<td>230</td>
<td>C$_6$H$_8$OH</td>
<td>60</td>
<td>C$<em>{10}$H$</em>{12}$N$_4$O$_2$</td>
<td>21.02</td>
</tr>
<tr>
<td>$\Pi_e$</td>
<td>180</td>
<td>CH$_2$CO$_2$H</td>
<td>50</td>
<td>C$<em>{10}$H$</em>{12}$N$_4$O$_2$</td>
<td>20.64</td>
</tr>
<tr>
<td>$\Pi_f$</td>
<td>220</td>
<td>C$_6$H$_8$OH</td>
<td>60</td>
<td>C$<em>{10}$H$</em>{12}$N$_4$ClO**</td>
<td>16.04</td>
</tr>
<tr>
<td>$\Pi_g$</td>
<td>278</td>
<td>CH$_2$CO$_2$H</td>
<td>90</td>
<td>C$<em>{10}$H$</em>{12}$N$_4$O</td>
<td>21.79</td>
</tr>
<tr>
<td>V</td>
<td>240</td>
<td>C$_6$H$_8$OH</td>
<td>80</td>
<td>C$<em>{10}$H$</em>{12}$N$_4$O</td>
<td>29.29</td>
</tr>
<tr>
<td>VI</td>
<td>260</td>
<td>CH$_2$CO$_2$H</td>
<td>60</td>
<td>C$<em>{10}$H$</em>{12}$N$_4$O$_2$</td>
<td>19.60</td>
</tr>
<tr>
<td>VII</td>
<td>170</td>
<td>C$_6$H$_8$OH</td>
<td>60</td>
<td>C$<em>{10}$H$</em>{12}$N$_4$O</td>
<td>25.45</td>
</tr>
<tr>
<td>VIII</td>
<td>150</td>
<td>C$_6$H$_8$OH</td>
<td>90</td>
<td>C$<em>{10}$H$</em>{12}$N$_4$O</td>
<td>22.70</td>
</tr>
<tr>
<td>IX</td>
<td>80</td>
<td>C$_6$H$_8$OH, ether</td>
<td>50</td>
<td>C$<em>{10}$H$</em>{12}$N$_4$O$_2$</td>
<td>21.14</td>
</tr>
<tr>
<td>X</td>
<td>180-82</td>
<td>C$_6$H$_8$</td>
<td>80</td>
<td>C$<em>{10}$H$</em>{12}$N$_4$O</td>
<td>25.45</td>
</tr>
</tbody>
</table>

All the compounds gave satisfactory C, H analysis.

*Cl: Found, 11.20 %; Req.: 11.75 %

**Cl: Found, 9.9 % , Req.: 10.31 %

Pyrimidino (6,1-b) 1,2,4-triazine derivatives ($\Pi_{a,b}$) and 2-methyl-5 (5,6diphenyl-1,2,4-triazin-3-yl)Pyrimidin-4,6dione (IV):

A mixture of $\Pi_{a}$ or $\Pi_{b}$ and $\Pi_{d}$ (1.0 gm) and anhydr. NaOAc (2 gm.) in glacial acetic acid (50 ml) was heated under reflux for 3 hours. After cooling it was poured into crushed ice. The solid obtained was filtered, washed with water and recrystallised to give $\Pi_{a,b}$ and IV respectively (Table 1). IR spectrum of $\Pi_{a}$ shows absorption bounds at 3020 - 2980 cm$^{-1}$(CH), 2220 cm$^{-1}$(C$\equiv$N), 1680 cm$^{-1}$ (C=O cyclic) and 1600 cm$^{-1}$(C=0).

Reduction of $\Pi_a$-Formation of V:

A mixture of $\Pi_a$ (1.0 gm) and zinc dust (1.0 gm.) in ethanol (10 ml.) and acetic acid (10 ml.) was heated under reflux for one hr., filtered while hot then concentrated. The solid obtained was recrystallized to give V (Table 1). I.R. of V shows abs. bonds at 3400 cm$^{-1}$ (NH$_2$), 3100 cm$^{-1}$(NH), 2950 cm$^{-1}$(CH$_2$) and 1660 cm$^{-1}$(C=0).
2-Methyl-5 (4,5-dihydro-5,6-diphenyl-1,2,4-triazin-3-yl) 6 (2 H)- Pyrimidin-4-one (VI):

A mixture of V (2 gm.) and anhyd. NaOAc (3 gm.) in glacial acetic acid (50 ml.) was refluxed for 4 hours, cooled and diluted with water. The solid obtained was isolated and recrystallized to give VI (Table 1).

Cyanoacetic acid hydrazide derivative (VII):

A mixture of equimolecular amounts of I and cyanoacetic acid hydrazide in dry pyridine (40 ml.), was heated under reflux for 1 hr. The reaction mixture was cooled then acidified (dil HCl) and the solid obtained was recrystallized to give VII (Table 1). I.R. of VII shows abs. bands at 3400 cm⁻¹(NH₂), 3250 cm⁻¹(NH), 2220 cm⁻¹ (C≡N) and 1690 cm⁻¹(C=O cyclic).

Condensation of VII with acetone - Formation of VIII:

A mixture of VII (0.01 M) and acetone (0.01 M) in absolute ethanol (100 ml.) was refluxed for half hour, cooled. The solid obtained was filtered and recrystallized to give VIII (Table 1).

4 (5,6-Diphenyl-1,2,4-triazin-3-yl) pyrazol-3,5-dione (IX):

A suspension of VII (2.0 gm.) in dilute hydrochloric acid (20 % 25 ml.) was heated under reflux for 5 hour, cooled and neutralized with aq. Na₂CO₃. The solid isolated was filtered and recrystallized to give IX (Table 1).

Reaction of I with cyanoacetic acid hydrazide-Formation of X:

A mixture of equimolecular amounts of I, cyanoacetic acid hydrazid and triethylamine in dry benzene (250 ml.) was heated under reflux on water-bath for 6 hrs., cooled then washed several times with water. The organic layer was concentrated. The solid isolated was recrystallized to give X (Table 1). I.R. of X shows abs. bands at 3200 cm⁻¹(NH), 2980 cm⁻¹, 2250 cm⁻¹(C≡N) and 1670 cm⁻¹(C=O). The nmr of X shows the important following signals:

i) Signal at (δ 3) characteristic for 2 H bonded to C≡N group.

ii) The signal at (δ 4.2) characteristic for active methylene group (NH-COCH₂⁻).

iii) The triplet centered at (δ. 7. 3) are probably the resonance of p-H of the phenyl groups.
Condensation of X with Vanilin-Formation of XI:

To a solution of X (0.01 M) in 50 ml of sodium ethylate solution (prepared by dissolving 0.23 gm. sodium in 20 ml abs. ethanol), the appropriate aldehyde (0.015 M) was added and the reaction mixture was refluxed for 1 hr. The solid obtained upon dilution and acidification was filtered and recrystallized to give XI (Table 2).

**TABLE 2**

**PHYSICAL DATA OF THE COMPOUND XI - XX**

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>M.P.°C</th>
<th>solvent</th>
<th>Yield %</th>
<th>Mol. Formula</th>
<th>Analysis of Nitrogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>XI</td>
<td>198-200</td>
<td>CH₃OH</td>
<td>90</td>
<td>C₆H₂₃N₂O₅</td>
<td>18.10/17.60</td>
</tr>
<tr>
<td>XII</td>
<td>195-97</td>
<td>CH₃CO₂H</td>
<td>60</td>
<td>C₆H₁₃N₂O₂</td>
<td>24.16/24.70</td>
</tr>
<tr>
<td>XIII</td>
<td>140</td>
<td>CH₃</td>
<td>90</td>
<td>C₆H₁₇N₄</td>
<td>35.12/34.90</td>
</tr>
<tr>
<td>XIV</td>
<td>240</td>
<td>CH₃CO₂H</td>
<td>60</td>
<td>C₆H₁₅N₄</td>
<td>24.19/23.50</td>
</tr>
<tr>
<td>XVIa</td>
<td>130</td>
<td>C₆H₇OH</td>
<td>80</td>
<td>C₆H₁₅N₂Cl₂*</td>
<td>17.81/17.19</td>
</tr>
<tr>
<td>XVIb</td>
<td>275</td>
<td>CH₃CO₂H</td>
<td>90</td>
<td>C₆H₁₇N₂O₂</td>
<td>19.08/18.80</td>
</tr>
<tr>
<td>XVIc</td>
<td>280</td>
<td>CH₃CO₂H</td>
<td>90</td>
<td>C₆H₁₅N₂O₂</td>
<td>18.27/18.20</td>
</tr>
<tr>
<td>XVIII</td>
<td>180</td>
<td>CH₃-pet. ether</td>
<td>60</td>
<td>C₆H₁₅N₂SO₄**</td>
<td>15.34/14.95</td>
</tr>
<tr>
<td>XIX</td>
<td>99</td>
<td>pet-ether 100-140</td>
<td>50</td>
<td>C₆H₁₅N₂O₂</td>
<td>18.35/18.20</td>
</tr>
<tr>
<td>XX</td>
<td>240-42</td>
<td>CH₃OH</td>
<td>90</td>
<td>C₆H₁₅N₂O₂</td>
<td>16.60/16.40</td>
</tr>
</tbody>
</table>

All the compounds gave satisfactory C,H analysis.
*Cl: Found, 26.80 %; Requir. 27.22
**S: Found, 6.80 %; Requir. 7.00.

1-(5,6-Diphenyl-1,2, -triazin-3-yl) 4 (2H)-pyrazol-3,5-dione (XII):

Compound X (3 gm.) in 2N sodium hydroxide solution (50 ml.) was refluxed for 4 hrs., cooled then neutralized with dilute hydrochloric acid. The solid obtained was filtered and recrystallized to give XII (Table 2). I.R. of XII shows abs. bands 3200 cm⁻¹(NH), 2900 cm⁻¹(CH) and 1670-1640 cm⁻¹(C=O).

Reaction of I and 2-hydrazinobenzimidazole-Formation XIII:

A mixture of I (0.01 M) and 2-hydrazinobenzimidazole (0.01 M) in dry pyridine was refluxed for one hr., cooled and acidified (dil. HCl). The solid obtained was filtered and recrystallized to give XIII (Table 2).

Cyclization of XIII-Formation of XIV:

A mixture of XIII (0.01 M), 1,2-dibromoethane (0.01 M) and ethanolic KOH (20 % - 50 ml) was refluxed for 2 hr., cooled and
filtered to remove the precipitated NaBr. The solid obtained upon dilution was filtered and recrystallized to give XIV (Table 2). I.R. of XIV shows abs. bands at 3200 - 3100 cm⁻¹(NH) and 1590 cm⁻¹ (C=–N). The U.V. spectrum of the compound XIV using ethanol as the solvent exhibited two main regions of absorption around 310 nm and 250 nm, characteristic of triazinyl substituted triazinobenzimidazol.

Reaction of I with aldehyde hydrazino derivative-Formation of alkylidene and arylidene derivatives XVIₐ₋ₑ:

A mixture of equimolecular amounts of I, the appropriate aldehyde hydrazine and triethylamine in dry benzene (300 ml.) was refluxed on a steam-bath for 6 hrs., cooled and washed several times with water. The orionic layer was concentrated. The solid isolated was filtered and recrystallized to give XVIₐ₋ₑ(Table 2). I.R. of XVIₑ shows abs. bands at 3500 cm⁻¹(OH), 3200-3150 cm⁻¹ bonded (NH), 1600 cm⁻¹(C=–N) and 1350 cm⁻¹(C–O stretching of phenols).

Reaction of XVIₑ with thioglycollic acid - Formation of XVIII:

A mixture of XVIₑ (0.01 M) and thioglycollic acid (0.015 M) in dry benzene (50 ml) was refluxed on water bath for 12 hrs. The reaction mixture was cooled and excess of benzene was removed under concentratred. The oil residue obtained was solidify with pet-ether (100-120). The solid obtained was filtered and crystallized to give XVII (Table 2). I.R. spectra of XVIII revealed strong band around 1700 cm⁻¹ (C=O), a medium band near 3320 cm⁻¹ (NH), bands around 1480 and 1185 cm⁻¹ (CH₂ and C-S groups.).

Reaction of I with N-acetyl, N-phenyl-hydrazine-Formation of XIX:

Equimolar (0.01 ml) mixture of I and the hydrazine was taken in dry pyridine (20 ml) and the reaction mixture was heated under reflux for 2 hr. Then the reaction mixture was cooled to room temperature, powered into dilute HCl. The solid obtained was washed with water and recrystallized to give XIX (Table 2). I.R. of XIX revealed abroad band at 3200 - 3100 cm⁻¹(NH), 3010-2980 cm⁻¹ (CH) and 1750 cm⁻¹(C=O).

Reduction of I-Formation of XX:

A mixture of I (2 gm) and zinc dust (5 gm.) in ethanol (25 ml) and acetic acid (25 ml) was heated under reflux for 4 hour, filtered while hot then concentrated. The solid obtained was recrystallized to give XIX Table 2).
Preparation of authentic sample—Reduction of 5,6-dipheyl-1,2,4-triazin-3-one (XXI):

A mixture of XXI (2 gm) and zinc dust (5 gm.) in ethanol (25 ml.) and acetic acid (25 ml.) was heated under reflux for 2 hr., filtered while hot then concentrated. The solid obtained was recrystallized to give XX. M. p. and m. m. p. gave no deps. I.R. of XX shows abs. bands at 3200 - 3100 cm\(^{-1}\) (NH) and 1700 cm\(^{-1}\) (C=O). U.V. of XIX using ethanol as solvent shows a region of absorption around 280 nm.

REFERENCES