Vicarious nucleophilic substitution of hydrogen vs. ANRORC-type ring transformation in reactions of 1,2,4-triazines with α-halocarbanions. Novel route to functionalized pyrazoles

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Dedicated to Professor Mieczyslaw Makosza on the occasion of his 70th birthday
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Abstract
A novel route to pyrazole derivatives bearing sulfonyl, aminosulfonyl, alkoxy- and aryloxy sulfanyl groups at C-3 by ring transformation of 3-chloro-6-aryl-1,2,4-triazines 1a-c with α-halocarbanions 2a-h is described.

Keywords: Ring transformation, 1,2,4-triazines, α-halocarbanions, pyrazoles

Introduction

Ring transformations of functionalized 1,2,4-triazines are valuable entries in the synthesis of several other heterocyclic systems. The triazines are frequently used as azadiene equivalents in the Diels-Alder cycloaddition/retro-cycloaddition reactions to form pyridine or pyrimidine derivatives.2 They also may undergo ring interconversions into five and six membered azaheterocycles when reacted with nucleophilic reagents.3 These transformations usually take place via several steps: (1) Addition of Nucleophile; (2) Ring Opening; and (3) Ring Closure of the resulting open-chain intermediate, [ANRORC mechanism]. An ANRORC – type mechanism has recently been observed when 3-X-1,2,4-triazines (X=nucleofugal group) react with activated methylene compounds, featuring the presence of cyano functionality at the carbanionic center. Functionalized 3-aminopyridazine derivatives are obtained.4 Such ANRORC – type ring transformations, initiated by the addition of the carbanionic center at C-5 may provide a new entry to the preparation of functionalized heterocycles, which could otherwise hardly be prepared by other methods.
It has also been observed that in the nucleophilic replacement of 3-X-1,2,4-triazines with potassium amide degenerate ring transformations occur, as proven by the observation that with $^{15}$N labeled potassium amide the 3-amino–1,2,4-triazines being formed are ring labeled (Scheme 1) [$S_N$ (ANRORC) mechanism].

$$\text{NH}_2\quad \text{N}$$
$$\text{N}$$
$$\text{N}$$
$$\text{X}$$
$$\text{R}_1\quad \text{R}_1\quad \text{R}_1\quad \text{R}_1$$

$^* = ^{15}$N
$R = R_1 = \text{H or Ph}$
$X = \text{Cl, Br, I, SMe, SO}_2\text{Me}$

Scheme 1

In this paper we describe a novel ring transformation being observed in reactions of 6-aryl-3-chloro-1,2,4-triazines (1a-c) with $\alpha$-chlorocarbanions derived from chloromethyl aryl sulfones (2a-d), chloromethyl $t$-Bu sulfone (2c), chloromethane sulfonamides (2d-f) and chloromethane alkyl- or arylsulfonates (2g-h) (Scheme 2).

$$\text{Ar}$$
$$\text{N}$$
$$\text{N}$$
$$\text{H}$$
$$\text{Cl}$$

1

$$\text{Ar}$$
$$\text{N}$$
$$\text{N}$$
$$\text{Cl}$$

2

$$\text{R}$$

3a-k

1  Ar
a  Ph
b  4-MeOC$_6$H$_4$
c  4-O$_2$NC$_6$H$_4$

2  R
a  4-MeC$_6$H$_4$
b  Ph
c  $t$-Bu
d  NMe$_2$
e  morpholino
f  piperidino
g  OCH$_2$C(Me)$_3$
h  OPh

Scheme 2
Results and Discussion

Reaction of 3-chloro-6-phenyl-1,2,4-triazine 1a with chloromethyl p-tolyl sulfone 2a in the presence of finely powdered potassium hydroxide in dimethylsulfoxide at room temperature gives 5-phenyl-3-p-tolylsulfonylpyrazole 3a in nearly quantitative yield (Scheme 2, Table 1). The structural assignment of 3a was based on its microanalysis, exact mass measurements, its IR spectrum featuring the presence of the NH group and its $^1$H NMR spectrum clearly showing the chemical shift of one singlet at $\delta=7.21$, attributed to the proton at C-4. Treatment of 1a with the sulfones 2b and 2c under the same reaction conditions as mentioned above affords the corresponding pyrazoles 3b and 3c, respectively, in reasonable yields (Table 1). Extending this study by using the chloromethane sulfonamides 2d-f clearly shows the generality of this ring contraction reactions, since in good yields the pyrazole 3-sulfonamides 3d-f are obtained. The neopentyl and phenyl ester of chloromethane sulfonic esters 2g-h, which are less stable in basic medium react smoothly with 1a affording the pyrazole 3-sulfonates 3g and 3h respectively (Table 1). The presence of a p-methoxy group in the phenyl group, i.e. 1b, has hardly any influence on the reaction course. Reaction of 1b with 2b and 2d gives the pyrazole 3i and 3j in acceptable yields (Table 1). In the reaction of 3-chloro-6-p-nitrophenyl-1,2,4-triazine 1c with the sulfone 2b the pyrazole 3k was obtained in only a very poor yield. However, when reaction of 1c with 2b was carried out in DMF at –10°C, the 5-(p-nitrophenyl)-3-(phenylsulfonyl)pyrazole 3k was obtained successfully (Table 1). Interestingly, under the applied reaction conditions no ipso substitution at C-3 was observed, although it is well known that 3-halo-1,2,4-triazines easily undergo ipso substitution with nucleophilic reagents (Table 1).3

Table 1. Ring transformation of 1,2,4-triazines 1 into pyrazoles 3 by $\alpha$-chlorocarbanions in the presence of powdered potassium hydroxide in DMSO at room temperature

<table>
<thead>
<tr>
<th>3</th>
<th>Ar</th>
<th>R</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Ph</td>
<td>4-MeC$_6$H$_4$</td>
<td>93</td>
</tr>
<tr>
<td>B</td>
<td>Ph</td>
<td>Ph</td>
<td>67</td>
</tr>
<tr>
<td>C</td>
<td>Ph</td>
<td>C(Me)$_3$</td>
<td>75</td>
</tr>
<tr>
<td>D</td>
<td>Ph</td>
<td>N(Me)$_2$</td>
<td>74</td>
</tr>
<tr>
<td>E</td>
<td>Ph</td>
<td>morpholino</td>
<td>67</td>
</tr>
<tr>
<td>F</td>
<td>Ph</td>
<td>pyrrolidino</td>
<td>82</td>
</tr>
<tr>
<td>G</td>
<td>Ph</td>
<td>OCH$_2$C(Me)$_3$</td>
<td>70</td>
</tr>
<tr>
<td>H</td>
<td>Ph</td>
<td>OPh</td>
<td>49</td>
</tr>
<tr>
<td>I</td>
<td>4-MeOC$_6$H$_4$</td>
<td>Ph</td>
<td>56</td>
</tr>
<tr>
<td>J</td>
<td>4-MeOC$_6$H$_4$</td>
<td>N(Me)$_2$</td>
<td>52</td>
</tr>
<tr>
<td>K</td>
<td>4-O$_2$NC$_6$H$_4$</td>
<td>Ph</td>
<td>55$^a$</td>
</tr>
</tbody>
</table>

$^a$ The reaction of 1c with 2b was carried out in DMF at -10°C.
Very surprisingly, a somewhat different reaction course was observed when instead of powdered potassium hydroxide in DMSO, potassium t-butoxide in DMSO was used as basic reagent. It was found that reaction of 3-chloro-6-phenyl-1,2,4-triazine 1a with sulfone 2a, using potassium t-butoxide at room temperature, yields besides the pyrazole 3a (40%), the vicarious substitution product 3-chloro-6-phenyl-5-[(p-tolylsulfonyl)methyl]-1,2,4-triazine 4 (16%) (Scheme 3, Table 2). This competition is strongly influenced by the base concentration. When base was added in portions to solution of 1a and 2a in DMSO the yield of 4 increased and the yield of 3a decreased (Table 2). When the same reaction was carried out with potassium t-butoxide in THF at -75°C, besides the products 3a and 4, 3-chloro-6-phenyl-5-[(p-tolylsulfonyl)methyl]-2,5-dihydro-1,2,4-triazine 5 was obtained, being a 1:1 mixture of diastereomers. If the ratio t-butoxide/1a is decreased below 1, pyrazole formation does not occur anymore and only the products 4 and 5 are formed (Table 2). From these results it is evident that competition between vicarious substitution and ring contraction strongly depends on the base used and the ratio substrate/base.

![Image of chemical structures](image)

**Scheme 3**

**Table 2.** Reaction of 3-chloro-6-phenyl-1,2,4-triazine 1a with chloromethyl tolyl sulfone 2a under various conditions

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Temperature [°C]</th>
<th>Amount of t-BuOK [mol/1mol 1a]</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMSO</td>
<td>20</td>
<td>2.5¹</td>
<td>40</td>
<td>16</td>
<td>-</td>
</tr>
<tr>
<td>DMSO</td>
<td>20</td>
<td>2.5²</td>
<td>24</td>
<td>28</td>
<td>-</td>
</tr>
<tr>
<td>THF</td>
<td>-75</td>
<td>2.5²</td>
<td>17</td>
<td>20</td>
<td>16</td>
</tr>
<tr>
<td>THF</td>
<td>-75</td>
<td>0.9²</td>
<td>-</td>
<td>22</td>
<td>23</td>
</tr>
</tbody>
</table>

¹ Mixture of substrates was added to the solution of t-BuOK.
² t-BuOK was added in portions to the solution of substrates.
Considering the mechanism of the formation of the products 3a, 4 and 5 it was proven that the pyrazoles are not formed by rearrangements of the vicarious product 4, since treatment of 4 with base did not give any pyrazole formation. Only starting material could be recovered. It is reasonable to assume the initial step is the formation of the anionic σH-adduct 6, since it has been shown that a THF solution of 1a, to which a THF solution of the anion of 2a was added dropwise at −75°C, only contained the anionic σH-adduct 6, being isolated as the 2,5-dihydroadduct 5. If this σH-adduct 6 is warmed to -20°C and stirred at this temperature for half an hour, the VNS product 4 and 2,5-dihydroadduct 5 are formed in 43 and 32% yield respectively. The formation of VNS product could be rationalized that one molecule of the σH-adduct plays role of base involving β-elimination of hydrochloric acid.

In this σH-adduct 6 two hydrogen atoms with different acidity are present, one at C-5 and the other one at the α position of the side-chain. The C-N bond breaking process taking place to obtain pyrazoles requires more drastic conditions (an excess of base, r.t.) than the loss of hydrochloric acid, leading to 4 (Scheme 4, route a). Therefore pyrazole formation cannot be expected to occur at the low temperature reactions without the base. After ring opening an intramolecular cyclisation takes place leading to an cyano derivatives of pyrazole. Hydrolysis and decarboxylation of the latter gives the required pyrazole 3 (Scheme 4, route b).

Scheme 4

The interesting observation was made that 1,2,4-triazine to pyrazole ring transformation strongly depends on the character on the leaving group at C-3. When in basic medium p-tolylsulfonyl 2a reacts for one hour with 6-phenyl-1,2,4-triazines 7a-d containing at C-3 a sulfur leaving group (SPh, SMe, SO2Ph, SO2Me) no pyrazole formation takes place, only the 2,5-dihydro-1,2,4-triazines 8 are obtained (Figure 1). Compounds 8a and 8b were obtained as
mixtures of diastereomers, whereas 8c and 8d appeared to be almost diastereometrically pure. Only traces of the minor stereoisomers were detected by $^1$H NMR.

$$\text{8a-d}$$

$$X=\text{SPh, SMe, SO}_2\text{Ph, SO}_2\text{Me}$$

Figure 1

In summary we have shown that reaction between “vicarious” carbanions 2a-h and 1,2,4-triazines 1a-c has a dual course leading to the formation of 5-substituted 1,2,4-triazine derivatives and/or ring contraction products i.e. pyrazoles depending on the reagents and reaction conditions.

Experimental Section

General Procedures. Reactions were monitored by TLC using precoated silica gel alumina plates containing a fluorescent indicator. Detection was done by uv (254 nm). Melting points were determined with a hot-stage microscope and are uncorrected. Column chromatography was performed on silica gel (Merck 60, 70–230 mesh). $^1$H NMR spectra were measured on a Varian Gemini (200 MHz) spectrometer using tetramethylsilane as an internal standard. Mass-spectra were measured on an AMD 604 spectrometer. The IR spectra were recorded on a Nicolet Impact 400 D spectrometer.

The starting materials were prepared according to known procedures: 3-chloro-6-phenyl-1,2,4-triazine (1a), chloromethyl tolyl sulfone (2a), chloromethyl phenyl sulfone (2b), chloromethyl $t$-Bu sulfone (2c), $N,N$-dimethyl(chloromethane)sulfonamide (2d), chloromethanesulfonic morpholide (2e), chloromethanesulfonic piperidide (2f), neopentyl chloromethanesulfonate (2g), phenyl chloromethanesulfonate (2h), 3-phenylsulfanyl-1,2,4-triazine (7a), 3-methylsulfanyl-1,2,4-triazine (7b), 3-phenylsulfonyl-6-phenyl-1,2,4-triazine (7c) and 3-methylsulfonyl-6-phenyl-1,2,4-triazine (7d).

General procedure for 3-chloro-6-(4-methoxyphenyl)-1,2,4-triazine (1b) and 3-chloro-6-(4-nitrophenyl)-1,2,4-triazine (1c)

6-(4-Methoxyphenyl)-3-hydroxy-1,2,4-triazine or 6-(4-nitrophenyl)-3-hydroxy-1,2,4-triazine (2 g) and phosphorus oxychloride (20 ml) was heated at 105°C for 40 min. The solution was evaporated under reduced pressure. Water and ice were added to the residue. The obtained precipitate was filtered and washed with water.
3-Chloro-6-(4-methoxyphenyl)-1,2,4-triazine (1b). The crude solid was refluxed with petroleum ether (3x50ml) to yield 1b as yellow needles after cooling. Yield 0.52g, 24%; mp 143-144°C; δH (200MHz, CDCl3) 3.90 (s, 3H, OCH3), 7.05 (d, 2H, J = 9.02), 8.05 (d, 2H, J = 9.02) 8.84 (s, 1H, Hhet); Anal. Calcd. for C10H8N3ClO (221.65): C 54.19, H 3.64, N 18.96, Found: C 54.10, H 3.56, N 18.88.

3-Chloro-6-(p-nitrophenyl)-1,2,4-triazine (1c). The crude solid was refluxed with chloroform (3x50ml). The solvent was evaporated and the product was purified by chromatography (chloroform:acetone, 100:1) to yield 1c as yellow needles. Yield 0.43 g, 20 %; mp 242-243°C; δH (200MHz, CDCl3) 8.29 (d, 2H, J = 9.12), 8.45 (d, 2H, J = 9.09); Anal. Calcd. for C9H5N4ClO2 (236.62): C 45.69, H 2.13, N 23.68, Found: C 45.39, H 1.98, N 23.46.

General procedure for ring transformation of 1,2,4-triazines 1 into pyrazoles 3
A solution of 6-aryl-3-chloro-1,2,4-triazine 1a-c (1 mmol) and the corresponding α-chlorocarbanions 2a-h (1.1 mmol) in DMSO (12 ml) was added dropwise to a vigorously stirred suspension of finely powdered KOH (1 g) in DMSO (6 ml) at room temperature. The reaction mixture was stirred at this temperature for 1 h, then poured into ice/water and neutralized with acetic acid. The precipitated solid was filtered, washed with water, purified by column chromatography (chloroform:acetone, 50:1) and recrystallized from ethanol/water.

3-p-Tolysulfonyl-5-(phenyl)pyrazole (3a). 0.277 g, 93 %; mp 147-148°C; νmax (KBr) 3300 (NH), 1320 (SO2), 1150 (SO2) cm⁻¹; δH (200 MHz, CDCl3) 2.42 (3 H, s, CH3), 13.60 (1 H, s, NH), 7.21 (1 H, s, Hhet), 7.30-7.80 (9 H, m, Haromatic); Anal. Calcd. for C16H14N2O2S (298.37): C, 64.41; H, 4.73; N, 9.39. Found: C, 64.46; H, 4.63; N, 9.40.

5-Phenyl-3-(phenylsulfonyl)pyrazole (3b). 0.190 g, 67 %; mp 153-154°C; νmax (KBr) 3300 (NH), 1310 (SO2), 1160 (SO2) cm⁻¹; δH (200 MHz, CDCl3) 7.26 (1 H, s, Hhet), 7.30-8.10 (10 H, m, Haromatic), 13.86 (1 H, s, NH); Anal. Calcd. for C15H12N2O2S (284.34): C, 63.36; H, 4.25; N, 9.85. Found: C, 63.12; H, 3.96; N, 10.15.

5-Phenyl-3-(t-butylsulfonyl)pyrazole (3c). 0.198 g, 75 %; mp 227-228°C; νmax (KBr) 3270 (NH), 1310 (SO2), 1120 (SO2) cm⁻¹; δH (200 MHz, CDCl3) 1.37 (9 H, s, C(Me)3), 7.15 (1 H, s, Hhet), 7.39-7.56 (3 H, m, Haromatic), 7.84-7.90 (2 H, m, Haromatic), 13.43 (1 H, s, NH); Anal. Calcd. for C13H16N2O2S (264.35): C, 59.07; H, 6.10; N, 10.60. Found: C, 58.98; H, 5.96; N, 10.57.

N,N-Dimethyl-5-phenyl-1H-pyrazole-3-sulfonamide (3d). 0.185 g, 74 %; mp 210-221°C; νmax (KBr) 3300 (NH), 1340 (SO2), 1150 (SO2) cm⁻¹; δH (200 MHz, CDCl3) 2.72 (6 H, s, NMe2), 7.10 (1 H, s, Hhet), 7.39-8.10 (5 H, m, Haromatic); Anal. Calcd. for C11H13N3O2S (251.31): C, 52.57; H, 5.21; N, 16.72. Found: C, 52.64; H, 5.38; N, 16.48.

3-Morpholinosulfonyl-5-phenylpyrazole (3e). 0.196 g, 67 %; mp 189-190°C; νmax (KBr) 3300 (NH), 1330 (SO2), 1160 (SO2) cm⁻¹; δH (200 MHz, CDCl3) 2.23 (4 H, s, Hmorpholinyl), 3.78 (4 H, s, Hmorpholinyl), 6.93 (1 H, s, Hhet), 7.46-7.59 (5 H, m, Haromatic); Anal. Calcd. for C13H15N3O3S (293.35): C, 53.23; H, 5.15; N, 14.32. Found: C, 53.27; H, 5.17; N, 14.19.

5-Phenyl-3-pyrrolidinopyrazole (3f). 0.227 g, 82 %; mp 198-199°C; νmax (KBr) 3300 (NH), 1330 (SO2), 1150 (SO2) cm⁻¹; δH (200 MHz, CDCl3) 1.80 (4 H, s, Hmorpholinyl), 3.40 (4 H, s,
Reaction of 3-chloro-6-phenyl-1,2,4-triazine 1a with chloromethyl tolyl sulfone 2a in the presence of t-BuOK at room temperature

**Procedure A.** A solution of 3-chloro-6-phenyl-1,2,4-triazine (1a) (0.191 g, 1 mmol) and chloromethyl tolyl sulfone (2a) (0.205 g, 1 mmol) in DMSO (12 ml) was added dropwise to a solution of t-BuOK (0.280 g, 2.5 mmol) in DMSO (6 ml) at room temperature. The reaction mixture was stirred at this temperature for 1 h, then poured into ice/water and neutralized with acetic acid. The precipitated solid was filtered. Products were separated by column chromatography (chloroform:hexane,10:1) and recrystallized from ethanol. Yields of the resulting products 3a, 4 are presented in Table 2.

**Procedure B.** t-BuOK (0.280 g, 2.5 mmol) was added in portions to a solution of 3-chloro-6-phenyl-1,2,4-triazine (1a) (0.191 g, 1 mmol) and chloromethyl tolyl sulfone (2a) (0.205 g, 1 mmol) in DMSO (12 ml) at room temperature. The reaction mixture was stirred at this temperature for 1 h, then poured into ice/water and neutralized with acetic acid. The precipitated solid was filtered. Products were separated by column chromatography (chloroform:hexane,
100:1) and recrystallized from ethanol. Yield of the resulting products 3a and 4 are shown in Table 2.

### 3-Chloro-6-phenyl-5-(p-tolylsulfonyl)methyl-1,2,4-triazine (4).

- **mp**: 94-95 °C
- **ν<sub>max</sub> (KBr)**: 1350 (SO₂), 1160 (SO₂) cm⁻¹
- **δ<sub>H</sub> (200 MHz, DMSO-d₆)**: 2.42 (3 H, s, Me), 4.94 (2 H, s, CH₂), 7.32-7.60 (9 H, m, H aromatic)

**Anal. Calcd. for C₁₇H₁₄N₃ClO₂S (359.84):**

- **C**: 56.75
- **H**: 3.92
- **N**: 11.68

**Found:**

- **C**: 56.61
- **H**: 4.04
- **N**: 11.16

### Reaction of 3-chloro-6-phenyl-1,2,4-triazine 1a with chloromethyl tolyl sulfone 2a in the presence of t-BuOK at –75 °C

**Method A.**

- t-BuOK (0.280 g, 2.5 mmol) was added in portions to a solution of 3-chloro-6-phenyl-1,2,4-triazine (1a) (0.191 g, 1 mmol) and chloromethyl tolyl sulfone (2a) (0.205 g, 1 mmol) in THF (10 ml) at –75 °C. The reaction mixture was stirred at this temperature for 1 h, then quenched with hydrochloric acid in ethanol. The solvent was removed *in vacuo*. The products were isolated by column chromatography (chloroform:hexane,100:1) and recrystallized from ethanol. Yields of the resulting products 3a, 4 and 5 are shown in Table 2.

**Method B.**

The reaction was carried according to *Method A* using 3-chloro-6-phenyl-1,2,4-triazine (1a) (0.210 g, 1.1 mmol), chloromethyl tolyl sulfone (2a) (0.225 g, 1.1 mmol) and t-BuOK (0.101 g, 0.9 mmol). Yields of the resulting products 4 and 5 are shown in Table 2.

### Synthesis of 3-chloro-5-(chloro(p-tolylsulfonyl)methyl)-6-phenyl-2,5-dihydro-1,2,4-triazine (5).

Chloromethyl tolyl sulfone (2a) (0.133 g, 0.65 mmol) was added to a solution of t-BuOK (0.073 g, 0.65 mmol) in 4 ml THF at –75 °C under argon. The resulting potassium salt of carbanion was added to a solution of 3-chloro-6-phenyl-1,2,4-triazine (1a) (0.096, 0.5 mmol) in THF at –75 °C. The reaction mixture was stirred at this temperature for 15 min. under argon, then quenched with hydrochloric acid in ethanol. The solvent was removed *in vacuo*. The residue was extracted with methylene chloride. The product was purified by column chromatography (methylen chloride:hexane, 100:1), to give 0.179 g (90%) of 5, being a 1:1 mixture of diastereomers which was separated by thin layer chromatography (chloroform:hexane, 50:1) to form: 5a: mp 148-150 °C, ν<sub>max</sub> (KBr) 3280 (NH) cm⁻¹; δ<sub>H</sub> (200 MHz, CDCl₃) 1.8, 6.22 (1 H, d, J=1.8), 7.34 (2 H, d, J=8.0, C₆H₄), 7.44 (3 H, m, H aromatic), 7.71 (2 H, m, H aromatic) 7.92 (2 H, d, J=8.0, C₆H₄), 8.35 (1 H, s NH); 5b: mp 118-120 °C, ν<sub>max</sub> (KBr) 3280 (NH) cm⁻¹; δ<sub>H</sub> (200 MHz, CDCl₃) 1.8, 4.81 (1 H, d, J=6.3), 5.78 (1 H, d, J=6.3), 7.35 (2 H, d, J=8.4, C₆H₄), 7.43 (3 H, m, H aromatic), 7.74 (2 H, m, H aromatic), 7.85 (2 H, d, J=8.4, C₆H₄), 8.38 (1 H, s NH); Anal. Calcd. for C₁₇H₁₅N₃Cl₂O₂S (396.30): C, 51.52; H, 3.82; N, 10.60. Found: C, 51.52; H, 3.69; N, 9.78.

### Conversion of anionic σ<sup>H</sup> adduct 6 into VNS product 4 and dihydroadduct 5 at –20 °C.

Chloromethyl tolyl sulfone (2a) (0.133 g, 0.65 mmol) was added to a solution of t-BuOK (0.073 g, 0.65 mmol) in 4 ml THF at –75 °C under argon. The resulting potassium salt of carbanion was added to a solution of 3-chloro-6-phenyl-1,2,4-triazine (1a) (0.096, 0.5 mmol) in
THF at -75 °C. The reaction mixture was stirred at this temperature for 15 min. under argon. The mixture was warmed to –20 °C and kept at this temperature for half an hour, then quenched with hydrochloric acid in ethanol. The solvent was removed in vacuo. The residue was extracted with methylene chloride. Products were separated by column chromatography (methylene chloride:hexane, 100:1) to yield compounds 4 (43 %) and 5 (32 %) respectively.

General procedure for synthesis of 3-X-5-[chloro(p-tolylsulfonyl)methyl]-6-phenyl-2,5-dihydro-1,2,4-triazines 8a-d
t-BuOK (0.280 g, 2.5 mmol) was added in portions to a solution of chloromethyl tolyl sulfone (2a) (0.113 g, 0.55 mmol) and 6-phenyl-3-X-1,2,4-triazine (7a-d) (0.5 mmol) in DMF (5 ml) at –45 °C. The mixture was stirred at this temperature for 1 hour, then poured into ice/water and neutralized with acetic acid. The resulting solid was filtered and washed with water. The product was purified by column chromatography (chloroform) and recrystallized from ethanol.

6-Phenyl-3-phenylsulfanyl-5-[chloro(p-tolylsulfonyl)methyl]-2,5-dihydro-1,2,4-triazine (8a). 0.231 g, 99 %; mp 155-156 °C; \( \nu_{\text{max}} \) (KBr) 3320 (NH), 1340 (SO\(_2\)), 1169 (SO\(_2\)) cm\(^{-1}\); \( \delta_H \) (200 MHz, CDCl\(_3\)) 2.46 (3 H, s, Me), 2.47 (3 H, s, Me), 4.78 (1 H, d, \( J=8.19 \)), 5.56 (1 H, d, \( J=8.16 \)), 4.90 (1 H, d, \( J=2.40 \)), C\(_6\)H\(_4\), 6.09 (1 H, d, \( J=2.47 \)), 7.33-7.51 (m, H\(_{\text{aromatic}}\)), 7.54-7.71 (m, H\(_{\text{aromatic}}\)); Anal. Calcd. for C\(_{23}\)H\(_{20}\)N\(_3\)ClO\(_2\)S\(_2\) (470.02): C, 58.78; H, 4.29; N, 8.94. Found: C, 58.64; H, 4.34; N, 8.72.

6-Phenyl-3-methylsulfanyl-5-[chloro(p-tolylsulfonyl)methyl]-2,5-dihydro-1,2,4-triazine (8b). 0.159 g, 78 %; mp 171-172 °C; \( \nu_{\text{max}} \) (KBr) 3300 (NH), 1330 (SO\(_2\)), 1160 (SO\(_2\)) cm\(^{-1}\); \( \delta_H \) (200 MHz, CDCl\(_3\)) 2.09 (3 H, s, Me), 2.44 (3 H, s, Me), 2.48 (3 H, s, Me), 2.55 (3 H, s, Me), 4.79 (1 H, d, \( J=8.9 \)), 5.57 (1 H, d, \( J=9.07 \)), 4.91 (1 H, d, \( J=1.92 \)), 6.14 (1 H, d, \( J=1.87 \)), 7.33-7.44 (m, H\(_{\text{aromatic}}\)), 7.69-7.80 (m, H\(_{\text{aromatic}}\)), 7.90-7.94 (m, H\(_{\text{aromatic}}\)), 8.43 (1 H, s, NH).

6-Phenyl-3-phenylsulfonyl-5-[chloro(p-tolylsulfonyl)methyl]-2,5-dihydro-1,2,4-triazine (8c). 0.135, 54 %; mp 95-96 °C; \( \nu_{\text{max}} \) (KBr) 3280 (NH), 1340 (SO\(_2\)), 1160 (SO\(_2\)) cm\(^{-1}\); \( \delta_H \) (200 MHz, CDCl\(_3\)) 2.46 (3 H, s, Me), 4.49 (1 H, d, \( J=6.36 \)), 5.82 (1 H, d, \( J=6.39 \)), 7.31-7.40 (5 H, m, H\(_{\text{aromatic}}\)), 7.58-7.75 (7 H, m, H\(_{\text{aromatic}}\)), 8.03-8.07 (2 H, m, H\(_{\text{aromatic}}\)), 9.59 (1 H, s, NH); Anal. Calcd. for C\(_{23}\)H\(_{20}\)N\(_3\)ClO\(_2\)S\(_2\) (502.01): C, 55.03; H, 4.02; N, 8.37. Found: C, 55.27; H, 4.02; N, 8.41.

6-Phenyl-3-methylsulfonyl-5-[chloro(p-tolylsulfonyl)methyl]-2,5-dihydro-1,2,4-triazine (8d). 0.120 g, 51 %; mp 158-159 °C; \( \nu_{\text{max}} \) (KBr) 3280 (NH), 1330 (SO\(_2\)), 1150 (SO\(_2\)) cm\(^{-1}\); \( \delta_H \) (200 MHz, CDCl\(_3\)) 2.48 (3 H, s, Me), 3.55 (3 H, s, SMe), 4.64 (1 H, d, \( J=8.19 \)), 5.57 (1 H, d, \( J=8.17 \)), 7.33-7.51 (5 H, m, H\(_{\text{aromatic}}\)), 7.71-7.78 (2 H, m, H\(_{\text{aromatic}}\)), 7.84-7.88 (2 H, m, H\(_{\text{aromatic}}\)), 9.64 (1 H, s, NH); Anal. Calcd. for C\(_{18}\)H\(_{19}\)N\(_3\)ClO\(_4\)S\(_2\) (439.94): C, 49.14; H, 4.12; N, 9.55. Found: C, 48.97; H, 3.88; N, 8.62. HRMS (EI) Found [M+H\(^+\)]\(^+\) 440.062062; C\(_{18}\)H\(_{19}\)N\(_3\)ClO\(_4\)S\(_2\) requires 440.050548.
References