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[1]

Andrzej Rykowski,[a*] Ewa Wolinska,[a] Danuta Branowska,[a] and Henk C. Van der Plas[b]

[a] Department of Chemistry, University of Podlasie, 08-110 Siedlce, Poland
E-mail: rykowski@ap.siedlce.pl
[b] Laboratory of Organic Chemistry, Wageningen University, Dreijenplein 8,
6703 HB Wageningen, The Netherlands
E-mail: mien.henk@tiscali.nl

Abstract

A novel route to pyrazole derivatives bearing sulfonyl, aminosulfonyl, alkoxy- and aryloxysulfonyl 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.

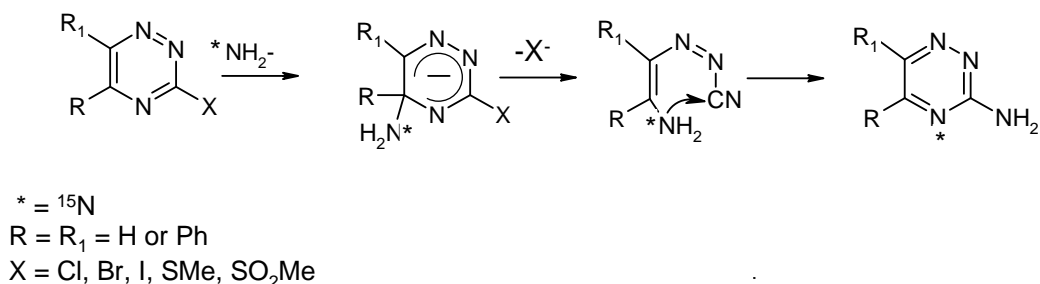**Keywords:** Ring transformation, 1,2,4-triazines, α-halocarbanions, pyrazoles
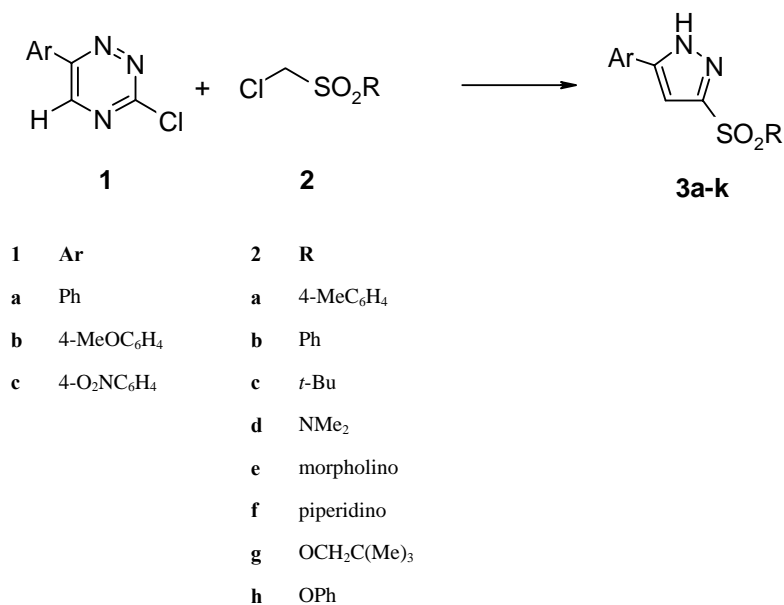
Introduction

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,[5] 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].

* = ^{15}N
R = R_1 = H or Ph
X = Cl, Br, I, SMe, SO_2Me

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 α-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).[6]

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

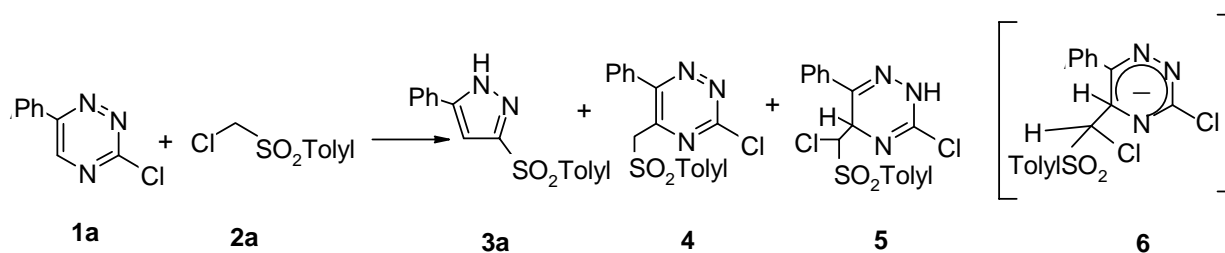**Scheme 2**

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 δ=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 (Table1). 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 α-chlorocarbanions in the presence of powdered potassium hydroxide in DMSO at room temperature

3	Ar	R	Yield %
A	Ph	4-MeC$_6$H$_4$	93
B	Ph	Ph	67
C	Ph	C(Me)$_3$	75
D	Ph	N(Me)$_2$	74
E	Ph	morpholino	67
F	Ph	pyrrolidino	82
G	Ph	OCH$_2$C(Me)$_3$	70
H	Ph	OPh	49
I	4-MeOC$_6$H$_4$	Ph	56
J	4-MeOC$_6$H$_4$	N(Me)$_2$	52
K	4-O$_2$NC$_6$H$_4$	Ph	55[a]

[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.

Scheme 3

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

Solvent	Temperature [°C]	Amount of *t*-BuOK [mol/1mol 1a]	3 %	4 %	5 %
DMSO	20	2.5[1]	40	16	-
DMSO	20	2.5[2]	24	28	-
THF	-75	2.5[2]	17	20	16
THF	-75	0.9[2]	-	22	23

[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 σ^H-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 σ^H-adduct **6**, being isolated as the 2,5-dihydroadduct **5**. If this σ^H-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 σ^H-adduct plays role of base involving β-elimination of hydrochloric acid.

In this σ^H-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).
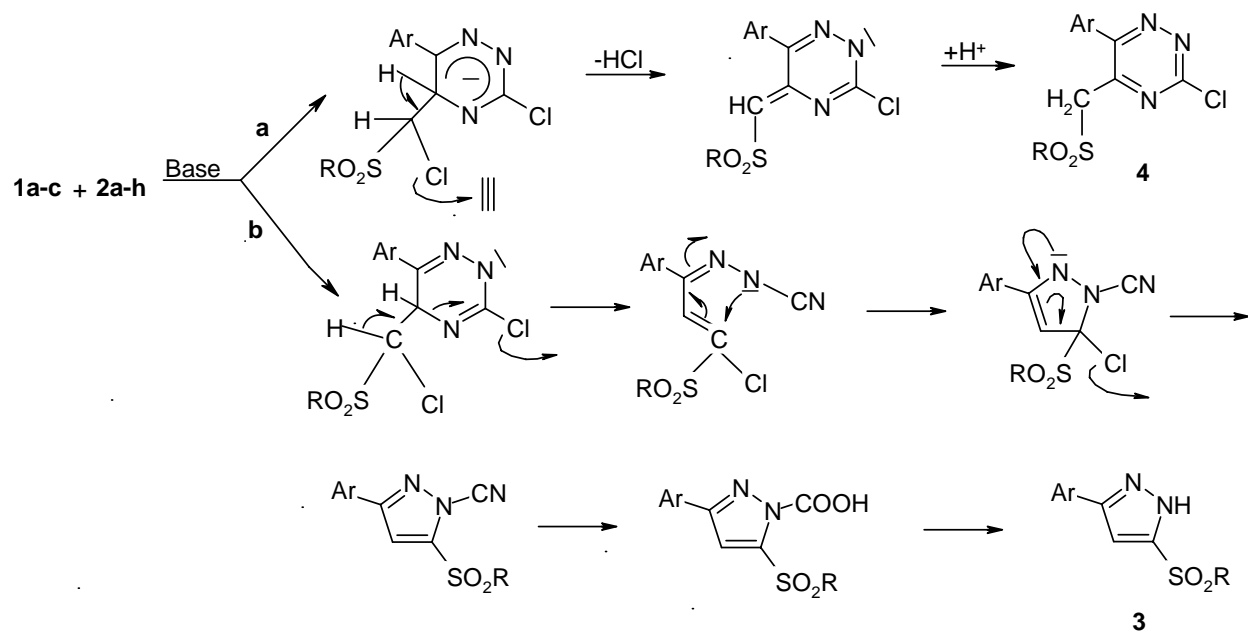
Scheme 4

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*-tolylsulfone **2a** reacts for one hour with 6-phenyl-1,2,4-triazines **7a-d** containing at C-3 a sulfur leaving group (SPh, SMe, SO$_2$Ph, SO$_2$Me) 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** appeard to be almost diastereometrically pure. Only traces of the minor stereoisomers were detected by ^{1}H NMR.
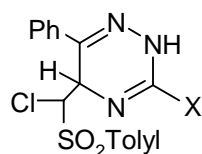
8a-d

X=SPh, SMe, SO$_2$Ph, SO$_2$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-substiuted 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 aluminia 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**),[7] chloromethyl tolyl sulfone (**2a**),[8] chloromethyl phenyl sulfone (**2b**),[9] chloromethyl *t*-Bu sulfone (**2c**),[10] *N,N*-dimethyl(chloromethane)sulfonamide (**2d**),[11] chloromethanesulfonic morpholide (**2e**),[12] chloromethanesulfonic piperidide (**2f**),[12] neopentyl chloromethanesulfonate (**2g**),[13] phenyl chloromethanesulfonate (**2h**),[13] 3-phenylsulfanyl-6-phenyl-1,2,4-triazine (**7a**),[14] 3-methylsulfanyl-6-phenyl-1,2,4-triazine(**7b**),[4c] 3-phenylsulfonyl-6-phenyl-1,2,4-triazine (**7c**)[4c] and 3-methylsulfonyl-6-phenyl-1,2,4-triazine (**7d**).[4c]

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 40min. 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; δ_H (200MHz, CDCl$_3$) 3.90 (s, 3H, OCH$_3$), 7.05 (d, 2H, J = 9.02), 8.05 (d, 2H, J = 9.02) 8.84 (s, 1H, H$_{het}$); Anal. Calcd. for C$_{10}$H$_8$N$_3$ClO (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, δ_H (200MHz, CDCl$_3$) 8.29 (d, 2H, J = 9.12), 8.45 (d, 2H, J = 9.09); Anal. Calcd. for C$_9$H$_5$N$_4$ClO$_2$ (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-Tolylsulfonyl-5-(phenyl)pyrazole (3a). 0.277 g, 93 %; mp 147-148 °C; ν_{max} (KBr) 3300 (NH), 1320 (SO$_2$), 1150 (SO$_2$) cm^{-1}; δ_H (200 MHz, CDCl$_3$) 2.42 (3 H, s, CH$_3$), 13.60 (1 H, s, NH), 7.21 (1 H, s, H$_{het}$), 7.30-7.80 (9 H, m, H$_{aromatic}$); Anal. Calcd. for C$_{16}$H$_{14}$N$_2$O$_2$S (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; ν_{max} (KBr) 3300 (NH), 1310 (SO$_2$), 1160 (SO$_2$) cm^{-1}; δ_H (200 MHz, CDCl$_3$) 7.26 (1 H, s, H$_{het}$), 7.30-8.10 (10 H, m, H$_{aromatic}$), 13.86 (1 H, s, NH); Anal. Calcd. for C$_{15}$H$_{12}$N$_2$O$_2$S (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; ν_{max} (KBr) 3270 (NH), 1310 (SO$_2$), 1120 (SO$_2$) cm^{-1}; δ_H (200 MHz, CDCl$_3$) 1.37 (9 H, s, C(Me)$_3$), 7.15 (1 H, s, H$_{het}$), 7.39-7.56 (3 H, m, H$_{aromatic}$), 7.84-7.90 (2 H, m, H$_{aromatic}$), 13.43 (1 H, s, NH); Anal. Calcd. for C$_{13}$H$_{16}$N$_2$O$_2$S (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-1*H*-pyrazole-3-sulfonamide (3d).** 0.185 g, 74 %; mp 210-221 °C; ν_{max} (KBr) 3300 (NH), 1340 (SO$_2$), 1150 (SO$_2$) cm^{-1}; δ_H (200 MHz, CDCl$_3$) 2.72 (6 H, s, NMe$_2$), 7.10 (1 H, s, H$_{het}$), 7.20-8.10 (5 H, m, H$_{aromatic}$); Anal. Calcd. for C$_{11}$H$_{13}$N$_3$O$_2$S (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; ν_{max} (KBr) 3300 (NH), 1330 (SO$_2$), 1160 (SO$_2$) cm^{-1}; δ_H (200 MHz, CDCl$_3$) 2.23 (4 H, s, H$_{morpholinyl}$), 3.78 (4 H, s, H$_{morpholinyl}$), 6.93 (1 H, s, H$_{het}$), 7.46-7.59 (5 H, m, H$_{aromatic}$); Anal. Calcd. for C$_{13}$H$_{15}$N$_3$O$_3$S (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; ν_{max} (KBr) 3300 (NH), 1330 (SO$_2$), 1150 (SO$_2$) cm^{-1}; δ_H (200 MHz, CDCl$_3$) 1.80 (4 H, s, H$_{morpholinyl}$), 3.40 (4 H, s,

H$_{morpholinyl}$), 6.96 (1 H, s, H$_{het}$), 7.26-7.39 (5 H, m, H$_{aromatic}$); Anal. Calcd. for C$_{13}$H$_{15}$N$_3$O$_2$S (277.35): C, 56.30; H, 5.45; N, 15.15. Found: C, 56.42; H, 5.44; N, 14.94.

3-Neopentyloxysulfonyl-5-phenylpyrazole (3g). 0.205 g, 70 %; mp 152-153 °C; ν_{max} (KBr) 3300 (NH), 1330 (SO$_2$), 1130 (SO$_2$) cm^{-1}; δ_H (200 MHz, CDCl$_3$) 0.88 (9 H, s, C(Me)$_3$), 3.82 (2 H, s, CH$_2$), 6.96 (1 H, s, H$_{het}$), 7.30-7.80 (5 H, m, H$_{aromatic}$), 14.10 (1 H, s, NH); Anal. Calcd. for C$_{14}$H$_{18}$N$_2$O$_3$S (294.38): C, 57.12; H, 6.16; N, 9.52. Found: C, 57.35; H, 6.20; N, 9.87.

5-Phenyl-3-(phenoxysulfonyl)pyrazole (3h). 0.147 g, 49 %; mp 128-129 °C; ν_{max} (KBr) 3300 (NH), 1370 (SO$_2$), 1140 (SO$_2$) cm^{-1}; δ_H (200 MHz, CDCl$_3$) 6.83 (1 H, s, H$_{het}$), 7.10-7.70 (10 H, m, H$_{aromatic}$); Anal. Calcd. for C$_{13}$H$_{15}$N$_3$O$_3$S (300.34): C, 59.99; H, 4.03; N, 9.33. Found: C, 59.87; H, 3.84; N, 9.50.

5-(*p*-Methoxyphenyl)-3-phenylsulfonylpyrazole (3i). 0.173 g, 56 %; mp 175-176 °C; ν_{max} (KBr) 3267 (NH), 1302 (SO$_2$), 1145 (SO$_2$) cm^{-1}; δ_H (200 MHz, CDCl$_3$) 3.79 (3 H, s, OMe) 7.02 (2 H, d, *J*=8.92, C$_6$H$_4$), 7.24 (1 H, s, H$_{het}$), 7.76-7.63 (5 H, m, H$_{aromatic}$), 7.95 (2 H, d, *J*=8.92, C$_6$H$_4$), 14.08 (1 H, s, NH); Anal. Calcd. for C$_{16}$H$_{14}$N$_2$O$_3$S (314.37): C, 61.13; H, 4.49; N, 8.91. Found: C, 61.13; H, 4.50; N, 8.83.

N,N-Dimethyl-5-(4-methoxyphenyl)-1*H*-pyrazole-3-sulfonamide (3j). 0.146 g, 52 %; mp 235-236 °C; ν_{max} (KBr) 3434 (NH), 1348 (SO$_2$), 1134 (SO$_2$) cm^{-1}; δ_H (200 MHz, CDCl) 2.71 (6 H, s, N(Me)$_2$), 3.80 (3 H, s, OMe) 7.04 (2 H, d, *J*=8.79, C$_6$H$_4$), 7.05 (1 H, s, H$_{het}$), 7.77 (2 H, d, *J*=8.82, C$_6$H$_4$), 14.02 (1 H, s, NH); Anal. Calcd. for C$_{12}$H$_{15}$N$_3$O$_3$S (281.34): C, 51.23; H, 5.37; N, 14.94. Found: C, 51.10; H, 5.22; N, 14.83.

5-(*p*-Nitrophenyl-3-(phenylsulfonyl)pyrazole (3k). 0.181 g, 55 %; mp 243 °C; ν_{max} (KBr) 3298 (NH), 1330 (SO$_2$), 1150 (SO$_2$) cm^{-1}; δ_H (200 MHz, CDCl$_3$) 7.66 (2 H, d, *J*=9.07, C$_6$H$_4$), 7.46 (1 H, s, H$_{het}$), 8.33 (2 H, d, *J*=9.07, C$_6$H$_4$), 8.02-8.15 (5 H, m, H$_{aromatic}$); HRMS (EI) Found [M]$^+$ 329.0485; C$_{15}$H$_{11}$N$_3$O$_4$S requires 329.0470.

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_{max} (KBr) 1350 (SO$_2$), 1160 (SO$_2$) cm^{-1}; δ_H (200 MHz, DMSO-d$_6$) 2.42 (3 H, s, Me) 4.94 (2 H, s, CH$_2$), 7.32-7.60 (9 H, m, H$_{aromatic}$); Anal. Calcd. for C$_{17}$H$_{14}$N$_3$ClO$_2$S (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 (methylene 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_{max} (KBr) 3280 (NH) cm^{-1}; δ_H (200 MHz, CDCl$_3$) 2.46 (3 H, s, Me), 4.92 (1 H, d, *J*=1.8), 6.22 (1 H, d, *J*=1.8), 7.34 (2 H, d, *J*=8.0, C$_6$H$_4$), 7.44 (3 H, m, H$_{aromatic}$), 7.71 (2 H, m, H$_{aromatic}$) 7.92 (2 H, d, *J*=8.0, C$_6$H$_4$), 8.35 (1 H, s NH); **5b**: mp 118-120 °C, ν_{max} (KBr) 3280 (NH) cm^{-1}; δ_H (200 MHz, CDCl$_3$) 2.46 (3 H, s, Me), 4.81 (1 H, d, *J*=6.3), 5.78 (1 H, d, *J*=6.3), 7.35 (2 H, d, *J*=8.4, C$_6$H$_4$), 7.43 (3 H, m, H$_{aromatic}$), 7.74 (2 H, m, H$_{aromatic}$), 7.85 (2 H, d, *J*=8.4, C$_6$H$_4$), 8.38 (1 H, s NH); Anal. Calcd. for C$_{17}$H$_{15}$N$_3$Cl$_2$O$_2$S (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^H 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, ν_{max} (KBr) 3320 (NH), 1340 (SO$_2$), 1169 (SO$_2$) cm^{-1}; δ_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$_{aromatic}$), 7.54-7.71 (m, H$_{aromatic}$), 7.81-7.93 (m, H$_{aromatic}$); 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, ν_{max} (KBr) 3300 (NH), 1330 (SO$_2$), 1160 (SO$_2$) cm^{-1}; δ_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$_{aromatic}$), 7.69-7.80 (m, H$_{aromatic}$), 7.90-7.94 (m, H$_{aromatic}$), 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, ν_{max} (KBr) 3280 (NH), 1340 (SO$_2$), 1160 (SO$_2$) cm^{-1}; δ_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$_{aromatic}$), 7.58-7.75 (7 H, m, H$_{aromatic}$), 8.03-8.07 (2 H, m, H$_{aromatic}$), 9.59 (1 H, s, NH); Anal. Calcd. for C$_{23}$H$_{20}$N$_3$ClO$_4$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, ν_{max} (KBr) 3280 (NH), 1330 (SO$_2$), 1150 (SO$_2$) cm^{-1}; δ_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$_{aromatic}$), 7.71-7.78 (2 H, m, H$_{aromatic}$), 7.84-7.88 (2 H, m, H$_{aromatic}$), 9.64 (1 H, s, NH); Anal. Calcd. for C$_{18}$H$_{18}$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

1. Part 23 in a series "1, 2, 4-Triazines in organic synthesis". For part 22 see Mojzych, M.; Rykowski, A. *Polish J. Chem.* In press.
2. Neunhoeffer, H. In *Comprehensive Heterocyclic Chemistry;* Katritzky, A. R., Ed.; Pergamon: Oxford, 1996; Vol.6, p 507.
3. Charushin, V. N.; Alexeev, S. G.; Chupakhin, O. N.; van der Plas, H. C. *Adv. Heterocycl. Chem.* **1989**, *46*, 73.
4. (a) Rykowski, A.; Wolinska, E. *Tetrahedron Lett.* **1996**, *37*, 5795. (b) Rykowski, A.; Wolinska, E.; van der Plas, H.C. *J. Heterocyclic Chem.* **2000**, *37*, 879. (c) Rykowski, A.; Wolinska, E.; van der Plas, H. C. *Chem. Heterocyclic Comp.* **2001**, *11*, 1549.
5. Van der Plas, H. C. A*dv. Heterocycl. Chem.* **1999**, *74*, 1.
6. Preliminary communication see: Rykowski, A.; Branowska, D. *Heterocycles* **1996**, *43*, 2095.
7. Trust, R.I.; Albright, J.D.; Lovel, F. M.; Perkinson, N. A. *J. Heterocycl. Chem.* **1979**, *16*, 1393.
8. Makosza, M.; Danikiewicz, W.; Wojciechowski, K. *Liebigs Ann. Chem.* **1987**, 711.
9. Makosza, M.; Golinski, J.; Baran, J. *J. Org. Chem.* **1984**, *49*, 1488.
10. Brown, M. S. *J. Org. Chem.* **1980**, *35*, 2831.
11. Jacobsen, H. J.; Senning, A.; Kaae, S. *Acta Chem. Scand.* **1971**, *25*, 3031.
12. Christensen, L. W.; Seman, J.E.; Truce, W. E. *J. Org. Chem.* **1973**, *38*, 2243.
13. Makosza, M.; Golinski, J. *Synthesis* **1983**, 1023.
14. Lalezari, L.; Golgolab, H. *J. Org. Chem.* **1970**, *7*, 689.