

**RING TRANSFORMATION OF 3-HALO-1,2,4-TRIAZINES WITH
 α -CHLOROCARBANIONS: A NOVEL ROUTE TO PYRAZOLES WITH
 SULFONYL, SULFONAMIDO AND SULFONYLOXY GROUPS¹**

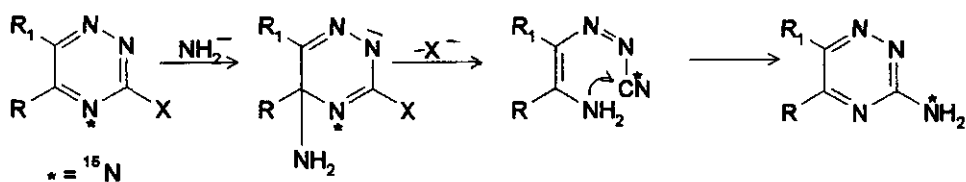
Andrzej Rykowski* and Danuta Branowska

Institute of Chemistry Agricultural University at Siedlce, 08-110 Siedlce, Poland

Abstract - A novel route to pyrazoles bearing sulfonyl, sulfonamido and sulfonyloxy groups at C-3 by ring cleavage reaction of 3-halo-6-phenyl-1,2,4-triazines (**1a-b**) with α -halocarbanions (**2a-g**) is described.

1,2,4-Triazines are useful synthetic intermediates particularly as heterocyclic azadienes in inverse electron demand Diels-Alder reaction.² They are also very susceptible to attack by all kinds of nucleophiles, leading to addition and subsequently either substitution or ring cleavage.³ The latter process takes place during amination of 1,2,4-triazines with potassium amide in liquid ammonia. Detailed studies of the mechanism of the amination of 5- or 6-substituted 3-X-1,2,4-triazines (X=leaving group) have shown that the formation of the corresponding 3-amino-1,2,4-triazines occur, to a great extent, according to the ANRORC mechanism⁴ involving an open-chain intermediate, as shown in Scheme 1.

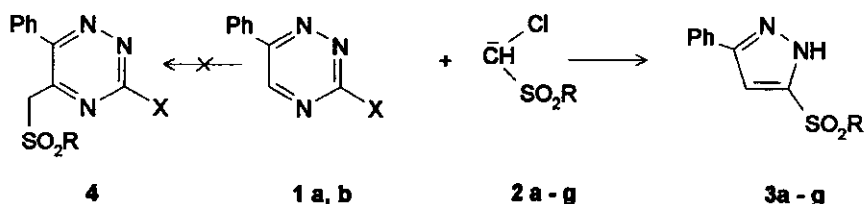
Scheme 1



Most substitutions which involve ring opening are achieved with powerful nitrogen nucleophiles. This ring-opening reaction opens a new access to preparation of functionalized heterocycles *via* ring transformation of 1,2,4-triazines. The facile ring cleavage of such systems by nucleophilic species prompted us to look into the possibility of ring-opening reactions by carbon nucleophiles, with different functionality, on carbanionic

centers. Previously, we have shown that 3-substituted 1,2,4-triazines with a free 5-position easily undergo the vicarious nucleophilic substitution of hydrogen (VNS) at C-5 when reacting with α -chlorocarbanions derived from chloromethyl *p*-tolyl sulfone (**2a**) and its analogues (**2b-g**).⁵ Herein, we wish to describe the finding that the reaction between "vicarious" carbanions (**2a-g**) and 3-halo-1,2,4-triazines (**1a-b**) takes a different course, not leading to the formation of 5-substituted 3-halo-1,2,4-triazines (**4**), but to ring contraction products, i.e., pyrazoles (**3a-g**) in synthetically useful yields (Scheme 2).

Scheme 2



When 3-chloro-6-phenyl-1,2,4-triazine (**1a**) reacts with 1.1 equiv of chloromethyl *p*-tolyl sulfone (**2a**) in dimethyl sulfoxide for 1 h at room temperature in the presence of powdered potassium hydroxide and the reaction mixture is poured into acidified ice-water, 3-phenyl-5-tosylpyrazole (**3a**) is formed in nearly quantitative yield. Chloromethyl phenyl sulfone (**2b**) and *N,N*-dimethyl chloromethanesulfonamide (**2c**) react efficiently with **1a** under the same reaction conditions, giving exclusively the ring contraction products (**3b**) and (**3c**). Similar behaviour was observed with **2d** and **2e**, although reactions of these carbanions with **1a** proceeded more slowly and with a somewhat lower yield. Phenyl chloromethanesulfonate (**2f**) and neopentyl chloromethanesulfonate (**2g**), which is less stable in basic medium, react smoothly with **1a** to afford the corresponding sulfonates (**3f**) and (**3g**) as the only reaction products. It is interesting to note that chloro substituent in **1a** which easily undergoes nucleophilic replacements *via* an addition-elimination mechanism,⁶ was not substituted by α -chlorocarbanions. However, reaction of more reactive 3-fluoro-6-phenyl-1,2,4-triazine (**1b**) with chloromethyl *p*-tolyl sulfone (**2a**) under the same reaction conditions gave pyrazole (**3a**) in poor yield in addition to 6-phenyl-1,2,4-triazin-3-one (**5**).⁶ The latter product (**5**) was obviously formed by conventional nucleophilic replacement of fluorine. Results of the reactions of carbanions (**2a-g**) with 2-halo-1,2,4-triazines (**2a-b**) are given in Table 1.

Table 1. Yields, melting points, ir and ^1H nmr data of compounds (**3a-g**)

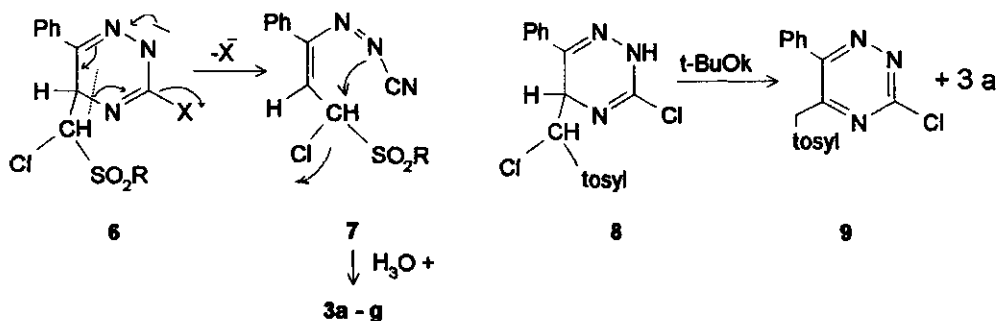
3	R	yield ^{a)}	mp °C	ir cm^{-1}	nmr δ ppm (CDCl_3)	
		%			(KBr)	C ₄ -H
a	$-\text{C}_6\text{H}_5\text{-CH}_3\text{-}p$	93 ^{b)}	147-148	3250	7.21	13.6
b	$-\text{C}_6\text{H}_5$	67	153-154	3300	7.26	13.8
c	$-\text{N}(\text{CH}_3)_2$	74	210-211	3300	7.10	13.7
d	4-morpholinyl	61	189-190	3250	6.93	13.7
e	1-pyrrolidinyl	55	198-199	3300	6.96	13.6
f	$-\text{OC}_6\text{H}_5$	47	128-129	3300	6.83	13.6
g	$-\text{OCH}_2\text{-C}(\text{CH}_3)_3$	70	152-153	3250	6.96	14.1

a) Reaction with **1a**.

b) Compound (**3a**) was prepared from **1b** and **2a** in 22% yield;

The results obtained in this study seem to justify the conclusion that 5-unsubstituted 1,2,4-triazines which contain a good leaving group at C-3 prefer ring contraction into pyrazole rather than VNS of hydrogen at C-5 when reacting with α -chlorocarbaniions.

Scheme 3



From the structure of the products, it is evident that the formation of **3a-g** proceeds *via* an initial addition of carbanion at C-5 in **1**. This leads to adduct (**6**), ring-opening with breaking of the 4,5-bond and intramolecular ring closure of the resulting open chain intermediate (**7**). The latter process involves nucleophilic replacement of chlorine by nitrogen followed by hydrolysis and decarboxylation of the cyano group (Scheme 3). To prove this three step mechanism the reaction of **1a** with **2a** was carried out in THF at -78°C in the presence of 1.5

equiv of potassium *tert*-butoxide. Under these conditions, compound (**1a**) forms a stable σ -adduct, which could be isolated in the pure state as dihydro 1,2,4-triazine (**8**) (66%) upon treatment with ammonium chloride.⁷ Compound (**8**) being a 1:1 mixture of diastereomers (**8a**) and (**8b**), easily separated by preparative tlc (silica gel - chloroform), undergoes ring contraction into **3a** (20%) and VNS of hydrogen at C-5 to form 3-chloro-6-phenyl-5-tosylmethyl-1,2,4-triazine (**9**) (19%)⁸ when reacting with an excess of potassium *tert*-butoxide in THF at room temperature. We are currently exploring the scope and limitations of this reaction in the preparation of several other heterocyclic systems from 1,2,4-triazines.

ACKNOWLEDGMENTS

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7. **8a**: mp 148-150°C. Ir ν (cm⁻¹) 3280. ¹H Nmr (CDCl₃) δ 8.35(s, 1H, NH), 7.92(d, 2H, J=8 Hz, tolyl H-2,6), 7.71(m, 2H, Ph H-2,6), 7.44(m, 3H, Ph H-3,4,5), 7.34(d, 2H, J=8 Hz, tolyl H-3,5), 6.22(d, 1H, J=1.8 Hz, CHCl), 4.92(d, 1H, J=1.8 Hz, H-5), 2.46(s, 3H, CH₃). FAB - ms m/z: 396 (MH)⁺, HR FAB - ms m/z: Calcd for C₁₇H₁₆N₃O₂Cl₂S (MH)⁺: 396.0340. Found: 396.0365. **8b**: mp 118-120°C. Ir ν (cm⁻¹) 3280. ¹H Nmr (CDCl₃) δ 8.38 (s, 1H, NH), 7.85(d, 2H, J=8.4 Hz, tolyl H-2,6), 7.74(m, 2H, Ph, H-2,6), 7.43(m, 3H, Ph H-3,4,5), 7.35(d, 2H, J=8.4 Hz, tolyl H-3,5), 5.78(d, 1H, J=6.3 Hz, CHCl), 4.81(d, 1H, J=6.3 Hz, H-5), 2.46(s, 3H, CH₃). FAB-ms m/z: 396 (MH)⁺. HR FAB-ms m/z: Calcd for C₁₇H₁₆N₃O₂Cl₂S (MH)⁺: 396.0340. Found: 396.0345.
8. **9**: mp 94-94°C. ¹H Nmr(CDCl₃) δ 7.21-7.75(m, 9H, Ph, tolyl), 4.65(s, 2H, CH₂), 2.41(s, 3H, CH₃). Anal. Calcd for C₁₇H₁₄N₃O₂Cl₂S: C 56.75; H 3.89; N 11.68. Found C 56.61; H 4.04; N 11.61.