RING TRANSFORMATION OF 3-HALO-1,2,4-TRIAZINES WITH 
\( \alpha \)-CHLOROCARBANIONS: A NOVEL ROUTE TO PYRAZOLES WITH 
SULFONYL, SULFONAMIDO AND SULFONYLOXY GROUPS

Andrzej Rykowski* and Danuta Branowska

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

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

1,2,4-Triazines are useful synthetic intermediates particularly as heterocyclic azadienes in inverse electron demand Diels-Alder reaction. They are also very susceptible to attack by all kinds of nucleophiles, leading to addition and subsequently either substitution or ring cleavage. 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 mechanism 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). 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, 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). 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 \textsuperscript{1}H nmr data of compounds (3a-g)

<table>
<thead>
<tr>
<th>3</th>
<th>( R )</th>
<th>yield\textsuperscript{a)}</th>
<th>mp ( ^\circ C )</th>
<th>ir cm\textsuperscript{-1}</th>
<th>nmr ( \delta ) ppm (CDCl\textsubscript{3})</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>(-C_6H_5-CH_3-p)</td>
<td>93\textsuperscript{b)}</td>
<td>147-148</td>
<td>3250</td>
<td>7.21</td>
</tr>
<tr>
<td>b</td>
<td>(-C_6H_5)</td>
<td>67</td>
<td>153-154</td>
<td>3300</td>
<td>7.26</td>
</tr>
<tr>
<td>c</td>
<td>(-N(CH_3)_2)</td>
<td>74</td>
<td>210-211</td>
<td>3300</td>
<td>7.10</td>
</tr>
<tr>
<td>d</td>
<td>4-morpholinyl</td>
<td>61</td>
<td>189-190</td>
<td>3250</td>
<td>6.93</td>
</tr>
<tr>
<td>e</td>
<td>1-pyrrolidinyl</td>
<td>55</td>
<td>198-199</td>
<td>3300</td>
<td>6.96</td>
</tr>
<tr>
<td>f</td>
<td>(-OC_6H_5)</td>
<td>47</td>
<td>128-129</td>
<td>3300</td>
<td>6.83</td>
</tr>
<tr>
<td>g</td>
<td>(-OCH_2-C(CH_3)_3)</td>
<td>70</td>
<td>152-153</td>
<td>3250</td>
<td>6.96</td>
</tr>
</tbody>
</table>

\textsuperscript{a)} Reaction with 1a.

\textsuperscript{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 \( \alpha \)-chlorocarbanions.

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\textdegree 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. 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%) 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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REFERENCES AND NOTES
1. Part 5 in 1,2,4-triazines in organic synthesis.
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. Cald for C₁₇H₁₄N₃O₂Cl₂S: C 56.75; H 3. 89; N 11.68. Found C 56.61; H 4.04; N 11.61.

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