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

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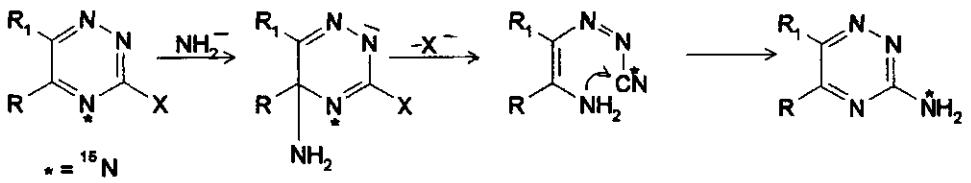
Abstract - A novel route to pyrazoles bearing sulfonyl, sulfonamido and sulfonyloxy groups at C-3 by ring cleavage reaction of 3-halo-6-phenyl-1,2,4-triazines (**1a-b**) with α- halocarbanions (**2a-g**) is described.

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 mechanism[4] involving an open-chain intermediate, as shown in Scheme 1.

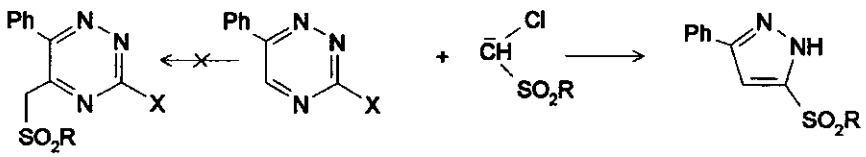
Scheme 1



Most substitutions which involve ring opening are achieved with powerful nitrogen nucleophiles. This ring-opening reaction opens a new acces 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



4 **1 a, b** **2 a - g** **3a - g**

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 ^{1}H nmr data of compounds (**3a-g**)

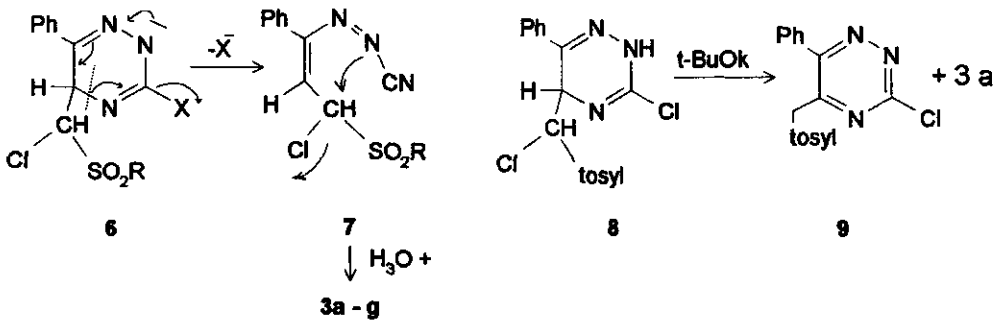
3	R	yield[a] %	mp °C	ir cm^{-1} (KBr)	nmr δ ppm ($CDCl_3$) C_4-H	N-H
a	-C_6H_5-CH_3-*p*	93[b]	147-148	3250	7.21	13.6
b	-C_6H_5	67	153-154	3300	7.26	13.8
c	-$N(CH_3)_2$	74	210-211	3300	7.10	13.7
d	4-morpholinyl	61	189-190	3250	6.93	13.7
e	1-pyrrolidinyl	55	198-199	3300	6.96	13.6
f	-OC_6H_5	47	128-129	3300	6.83	13.6
g	-OCH_2-$C(CH_3)_3$	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-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 (Scheme3). 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 ($CDCl_3$) 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, C**H**Cl), 4.92(d, 1H, J=1.8 Hz, H-5), 2.46(s, 3H, CH_3). FAB - ms m/z: 396 $(MH)^+$, HR FAB - ms m/z: Calcd for $C_{17}H_{16}N_3O_2Cl_2S$ $(MH)^+$: 396.0340. Found: 396.0365. **8b**: mp 118-120°C. Ir ν (cm^{-1}) 3280. ^1H Nmr ($CDCl_3$) 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, C**H**Cl), 4.81(d, 1H, J=6.3 Hz, H-5), 2.46(s, 3H, CH_3). FAB-ms m/z: 396 $(MH)^+$. HR FAB-ms m/z: Calcd for $C_{17}H_{16}N_3O_2Cl_2S$ $(MH)^+$: 396.0340. Found: 396.0345.

8. **9**: mp 94-94°C. ^1H Nmr($CDCl_3$) δ 7.21-7.75(m, 9H, Ph, tolyl), 4.65(s, 2H, CH_2), 2,41(s, 3H, CH_3). Anal. Cald for $C_{17}H_{14}N_3O_2Cl_2S$: C 56.75; H 3. 89: N 11.68. Found C 56.61; H 4.04; N 11.61.

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