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Ring Opening and Ring Closure Reactions of 1,2,4-Triazines with Carbon Nucleophiles: A Novel Route to Functionalized 3-Aminopyridazines[1]

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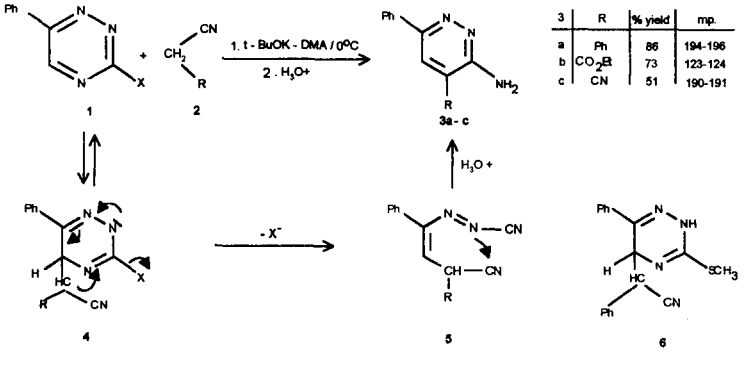
Abstract: A novel route to functionalized 3-aminopyridazines by reaction of 6-substituted 3-chloro-1,2,4- triazines with carbon nucleophiles bearing a cyano substituent at a carbanionic center was developed and a key part of the reaction mechanism was elucidated based on the results of studies using ^{15}N-labelled phenylacetonitrile Copyright © 1996 Elsevier Science Ltd

1,2,4-Triazines are useful intermediates in the synthesis of several other heterocyclic systems. They are well established as heterodienes in the inverse electron demand Diels-Alder reaction to form functionalized pyridine derivatives[2] and undergo ring interconversions into five and six membered aza heteroaromatics when reacted with nucleophilic reagents.[3] The ease with which the 1,2,4-triazine ring can be opened is well illustrated by reaction of substituted 1,2,4-triazines with potassium amide.[4] We have previously reported that conversion of 3-X-6-phenyl-1,2,4-triazines **1** (X=Cl, SCH_3) into corresponding 3-amino-6-phenyl-1,2,4-triazine with potassium amide in liquid ammonia occurs via a so-called ANRORC mechanism,[5] involving an initial addition of the amide ion at C-5, ring opening with scission of the 4,5-bond and ring closure. It has now become clear that such ring transformations of 1,2,4-triazines take place with activated methylene compounds bearing a cyano substituent at the nucleophilic carbon. In the present paper we describe a novel synthesis of functionalized 3-aminopyridazines, which are valuable substrates for fused heterocycles,[6] based on reaction of **1** with said carbon nucleophiles, and to propose the reaction mechanism (Scheme 1).

Scheme 1



3	R	% yield	mp.
a	Ph	86	194-196
b	CO_2R	73	123-124
c	CN	51	190-191

When compound **1** (X=Cl) reacts with 1.1 equiv of phenylacetonitrile **2** (R=Ph) in dry N,N-dimethylacetamide (DMA) at 0°C in the presence of an excess of potassium tert-butoxide for 1 h and the reaction mixture is poured into ice-water, 1,2-diaza-1,5-dicyano-3,4-diphenyl-1,3-pentadiene (**5** R=Ph) is formed in 86% yield. This compound is sufficiently stable to be isolated in pure state and to be fully characterized by elemental analysis and by ir, nmr and ms spectra.[7] The open chain product **5** is converted almost quantitatively into 3-amino-4,6-diphenylpyridazine (**3a**) upon treatment with 1:1 aqueous ammonia - acetone for 1 h. Compound **3a**, on the other hand, can be prepared directly from **1** (X=Cl) and phenylacetonitrile if reaction is carried out in N,N-dimethylformamide (DMF) under basic conditions, followed by neutralization with aqueous acetic acid. Ethyl cyanoacetate and malononitrile **2** ($R=CO_2Et$ or CN) react efficiently with **1** in DMA giving directly **3b** and **3c** in 73 and 51% yield. When the reactions of these carbanions with **1** are followed by TLC, it became evident, that in both reactions the corresponding open-chain intermediates **5** ($R=CO_2Et$ or CN) are formed, which quickly convert into 3-aminopyridazines **3b** and **3c** during work-up. This ring transformation of 1,2,4-triazine into pyridazine system is unprecedented. With regards to the mechanism of the conversion of **1** into **3** we assume that it proceeds via (i) an initial addition of carbanion at C-5, leading to adduct **4**, (ii) ring opening of **4** into **5** and (iii) intramolecular ring closure of the resulting open-chain intermediate **5**. To investigate the mechanism the reaction of **1** (X=Cl) was carried out with ^{15}N- phenylacetonitrile **2*** (7.0% excess of ^{15}N) in DMF under the conditions described previously to give 3-amino-4,6-diphenylpyridazine, **3***, containing a 7.1% excess of ^{15}N. This result allows us to conclude that the nitrogen atom of the exocyclic amino group of **3*** was originally present in the phenylacetonitrile and the cyano substituent attached to a nitrogen at position 1 of **5** was eliminated. The high susceptibility of C-5 in 1,2,4-triazine for nucleophilic addition of carbon nucleophiles was nicely demonstrated by the fact that **1** ($X=SCH_3$) undergoes covalent addition at C-5 with phenylacetonitrile to give a stable dihydro 1,2,4-triazine **6** in 53% yield as a mixture of diastereomers .[8] The results of further studies on the scope and the mechanism of this new reaction will be published.

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References and Notes.

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7. (**5** R=Ph) mp. 117-118°C; IR (KBr) ν 2260 cm^{-1} ; ^1H NMR (acetone-d_6, 200 MHz) δ 2.81 (s, 1H), 7.44-7.61 (m, 9H), 7.96-7.99 (m, 2H); HRMS calcd.for $C_{17}H_{12}N_4$ (M^+) 272. 1062, found 272. 1061.
8. (**6**) mp. 165-166°C; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.42 (s,3 H), 2.61 (s, 3H), 4.03 (d, 1H, J=9 Hz), 4.09 (d, 1H, J=6 Hz), 5.27 (d, 1H, J=9 Hz), 5.48 (d, 1H, J=6 Hz), 7.18-7.77 (m, 20 H), 7.82 (s, 1H, NH), 8.45 (s, 1H, NH).

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