A New Route to Functionalized 3-Aminopyridazines by ANRORC Type Ring Transformation of 1,2,4-Triazines with Carbon Nucleophiles [1]

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Dedicated to the memory of Professor Raymond N. Castle for his important contribution to heterocyclic chemistry and his dedication in serving the heterocyclic community

The reaction of 3-chloro-6-phenyl-1,2,4-triazine **1a** with carbon nucleophiles **2a-d** bearing a cyano substituent at a carbanionic center has been studied. In all reactions the formation of the corresponding 3-aminopyridazines **3a-d** takes place via ANRORC mechanism involving addition of the nucleophile at position 5 in compound **1a**, ring opening with breaking of the N_4-C_5 bond and intramolecular ring closure of the resulting open-chain intermediate. A ^{15}N study with labeled phenylacetonitrile **2a*** has shown that the nitrogen atom of the exocyclic amino group of 3-amino-4,6-diphenylpyridazine **3a** was originally present in phenylacetonitrile.

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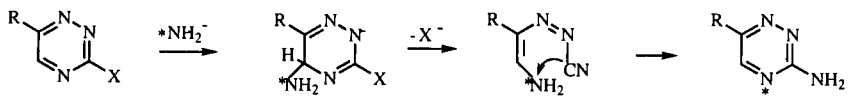
1,2,4-Triazines are frequently used as electron-deficient dienes in inverse electron demand Diels-Alder reactions [2]. Such reactions provide access to a host of novel pyridines or pyrimidines. There are also a number of reports on useful ring transformations of 1,2,4-triazines initiated by the addition of nucleophiles [3]. They can be exemplified by the high yield conversion of 1,2,4-triazines to imidazolin-2-ones or 1,2,3-triazoles on treatment with hydroxylamine-O-sulfonic acid or chloramine under basic conditions [4], by the formation of N-methyl 1,2,4-triazoles in reactions of 1-methyl-1,2,4-triazinium salts with alkali [5], or by the ring contraction of 6-substituted-3-halo-1,2,4-triazines to functionalized pyrazoles in reactions with α-chlorocarbanions [6]. The ease with which the 1,2,4-triazine ring can be opened is well illustrated by amination of 3-X-1,2,4-triazines (X = nucleophugic group) with ^{15}N labeled potassium amide in liquid ammonia [7,8] leading to 3-amino-6-phenyl[4-^{15}N]1,2,4-triazine (see Scheme 1).

In this paper we discuss a new ring transformation of 3-X-1,2,4-triazines (X = Cl, SCH_3), being observed in reactions of these triazines with several carbon nucleophiles, featuring the presence of a cyano functionality at the carbanionic centre [10].

When 3-chloro-6-phenyl-1,2,4-triazine **1a** is reacted with 1.1 equivalent of phenylacetonitrile **2a** in dry *N,N*-dimethylformamide (DMF) at 0° C in the presence of an excess of potassium *t*-butoxide for 1 hour and the reaction mixture is poured into ice-water, 3-amino-4,6-diphenylpyridazine **3a** is obtained in 62% yield together with traces of 3-(*N,N*-dimethylamino)-6-phenyl-1,2,4-triazine **4**. The latter compound is probably formed from **1a** by conventional nucleophilic replacement of chlorine with dimethylamine being present in the solution of potassium *t*-butoxide in DMF. When instead of DMF, *N,N*-dimethylacetamide (DMA) is used and the same reaction conditions were applied as mentioned above, 1,2-diaza-1,5-

Scheme 1

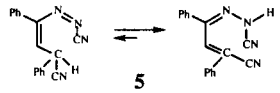


* = ^{15}N
X=Cl, SCH_3; R=H, Ph

This degenerate ring transformation can be described as a sequence of reactions involving Addition of Nucleophile, Ring Opening and intramolecular Ring Closure of the resulting open-chain intermediate (S_NAN-RORC mechanism) [9].

dicyano-3,4-diphenyl-1,3-pentadiene **5** is formed in 86% yield (see Figure 1). The compound is sufficiently stable to be isolated in pure state and could be characterized by ir, ^1H nmr, ms and hrms spectra. Compound **5** can exist as two tautomeric structures: **5a** and **5b**. The presence of a

singlet corresponding to an ethylene hydrogen in the ^1H nmr spectrum and the NH group in its ir spectrum allow us to conclude that structure **5b** must be the isomer isolated. Treatment of **5b** with base leads to ring closure to form **3a** (Table I).



5a **5** **5b**

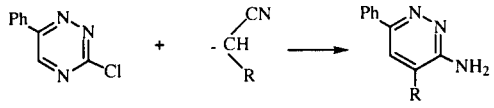
Figure 1

temperature conditions (-75 °C) were necessary in order to avoid a vicarious nucleophilic substitution (VNS) of the hydrogen at C-5, since compound **2d**, bearing a good leaving group on the carbanionic centre may induce a S_NH substitution in nitroarenes and electrophilic heterocycles [11]. Under the applied conditions VNS was not observed; only ring transformation of **1a** into 3-amino-6-phenyl-4-(phenylsulfonyl)pyridazine **3d** was found.

The results of the reactions of **1a** with derivatives of acetonitrile **2a-d** are summarized in Table I and Table II.

On the basis of our earlier studies [7,8] we propose the following mechanism for the ring transformation of

Table 1
The Yields and the Reaction Conditions for the Formation of 3-Aminopyridazines **3a-d**



1a **2a-d** **3a-d**

2	R	Temp. °C	Solvent	Product	% Yield
a	Ph	0	DMF	**3a**	62
a	Ph	0	DMA	**3a**	86 [a]
b	CO_2Et	0	DMA	**3b**	73
c	CN	0	DMA	**3c**	51
d	SO_2Ph	-75	THF	**3d**	60

[a] After treatment of **5b** with base.

Table 2
Spectroscopic Data of 3-Aminopyridazines **3a-d**

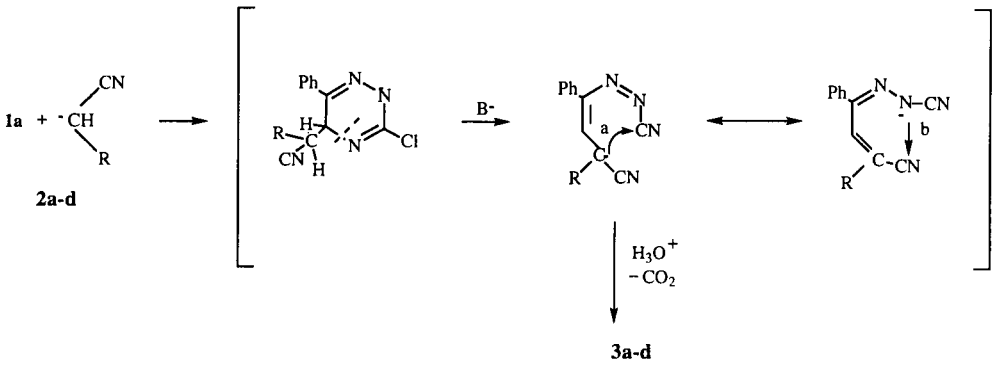
Compound	Mp °C	^1H NMR (deuteriochloroform) (δ, J in Hz)	IR cm^{-1}	MS (M^+)
3a	194-195 [a]	5.10 (s, 2H), 7.40-7.80 (m,11H)	3450, 1640	247
3b	123-124	1.44 (t, 3H, J=7), 4.45 (q, 2H, J=7) 6.51 (s, 2H), 7.45-8.02 (m, 5H), 8.16 (s, 1H),	3450, 1720 1650	243
3c	191-193	5.47 (s, 2H), 7.44-7.49 (m, 3H), 7.83 (s, 1H), 7.91-7.96 (m, 2H)	3450, 2260 1660	196
3d	192-194	6.12 (s, 2H), 7.47-8.00 (m, 10H), 8.13 (s, 1H)	3450, 1640 1360, 1330	311

[a] Lit. 194-196 °C, see ref. [16].

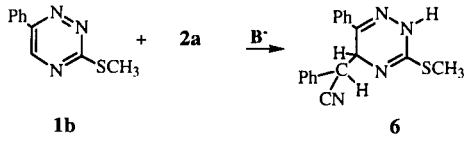
Ethyl cyanoacetate **2b** and malononitrile **2c** also react efficiently with **1a** in DMA giving directly **3b** and **3c** in 73 and 51% yield, respectively. When these reactions are followed by TLC, it becomes evident that in both reactions intermediates are formed which quickly convert to the corresponding 3-aminopyridazines **3b** and **3c** during work up. A similar transformation of the triazine ring also occurs in the reaction of **1a** with (phenylsulfonyl)acetonitrile **2d** in THF at -75 °C, 3-amino-6-phenyl-4-(phenylsulfonyl)pyridazine **3d** being obtained. These low 1,2,4-triazine **1a** into pyridazines **3a-d**. It is reasonable to assume that the reaction proceeds by an initial addition of the corresponding carbanion at position 5 in compound **1a**. After adduct formation, ring opening occurs with breaking of the N_4-C_5 bond, followed by intramolecular ring closure of the resulting open-chain intermediate, (ANRORC-mechanism). This ring closure can occur according to two different routes (route a or b, see Scheme 2).

To substantiate this proposed mechanism the following remarks can be made. Concerning the adduct formation it

Scheme 2



Scheme 3



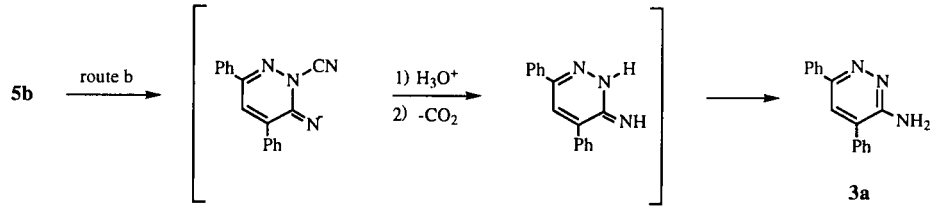
is known that C-5 in 1,2,4-triazine is highly susceptible for addition of carbon nucleophiles. This was nicely confirmed when 3-(methylthio)-6-phenyl-1,2,4-triazine **1b** was reacted with phenylacetonitrile **2a** in DMA at 0 °C in the presence of an excess of potassium *t*-butoxide. Under these reaction conditions compound **1b** undergoes covalent addition at C-5 with phenylacetonitrile to give, after neutralization, the stable dihydro compound **6** in good yield as a mixture of two diastereomers (see Scheme 3).

The structure assignment of **6** is based on its analysis, exact mass measurements ($C_{18}H_{16}N_4S$), its ir spectrum featuring the presence of the cyano (2250 cm^{-1}) and the NH group (3350 cm^{-1}) and the ^1H nmr spectrum clearly showing the chemical shifts and multiplicity pattern of a 2,5-dihydro-1,2,4-triazine [12, 13]. The ^1H nmr spectrum exhibited the pair of doublets at δ = 4.03 (J = 9 Hz) and at δ = 4.09 (J = 6 Hz) which can only correspond to the C-5 hydrogen in 1,2,4-triazine coupling with the proton of phenylacetonitrile. The latter resonates at lower field giving two doublets at δ = 5.27 and δ = 5.48. The NH signals for the two diastereomers appear at δ = 7.82 and δ = 8.45 respectively. These data are in good agreement with those reported earlier for 2,5-dihydro-3-(methylthio)-5-phenyl-1,2,4-triazine, obtained by sodium borohydride reduction of 3-(methylthio)-5-phenyl-1,2,4-triazine [12] and by Grignard reaction of 3-(methylthio)-1,2,4-triazine with phenyl magnesium bromide [13].

Concerning the ring opening and the ring closure we already mentioned the isolation of the dicyano compound **5b**, clearly showing the ring opening between N-4 and C-5. This compound is converted into 3-amino-4,6-diphenylpyridazine **3a** upon treatment with 1:1 aqueous ammonia/acetone for 1 hour. The result clearly shows that the open-chain intermediate **5b** is a reactive intermediate in the formation of **3a**; however it does not explain the course of the cyclization step.

In order to establish whether the formation of **3a** occurs by route a or by route b (see Scheme 2), we reacted 3-chloro-6-phenyl-1,2,4-triazine **1a** with ^{15}N labeled phenylacetonitrile in DMF under the conditions described previously. If route a is operative it will lead to 3-amino-4,6-diphenylpyridazine **3a** being ^{15}N unlabeled; in case of *r*oute b compound **3a** will contain the ^{15}N content in the exocyclic amino group (see Scheme 2). The ^{15}N labeled phenylacetonitrile **2a*** was prepared from benzyl bromide and ^{15}N potassium cyanide, and the ^{15}N content in compounds **2a*** and **3a*** was established by mass spectrometric determinations of the intensities of the M+1 and M peaks. Reaction of **1a** with **2a*** (containing 7.0% excess of ^{15}N) gave compound **3a*** in which 7.1% of an excess of ^{15}N is present. This result unequivocally proves that under basic conditions

Scheme 4



the open-chain intermediate **5** undergoes intramolecular ring closure *via* route b. It involves an initial addition of nitrogen to the nitrile carbon, followed by hydrolysis and decarboxylation of the N-cyano group during work up (Scheme 4). Further studies on the mechanism of this regiospecific ring closure reaction are in progress.

This ring transformation is the first example in which a C_5-N_4 fragment of the 1,2,4-triazine ring is replaced by the C-C fragment of an acetonitrile derivative, introducing at the same time an amino group at C-3.

EXPERIMENTAL

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 Kofler hot stage microscope and are uncorrected. The ir spectra were recorded on a Nicolet Impact 400 D spectrometer. The nmr spectra were recorded on Varian EM-360L or Varian 'Gemini' 2000 at 200 MHz using tetramethylsilane as an internal standard. Mass spectra were carried out with AMD 604 Inectra spectrometer. The ^{15}N measurements were carried out with an AE MS 902 spectrometer.

The starting materials were prepared according to known procedures: 3-chloro-6-phenyl-1,2,4-triazine **1a** [14] and 3-(methylthio)-6-phenyl-1,2,4-triazine **1b** [15].

3-Amino-4,6-diphenylpyridazine (**3a**).

Method a.

To a stirred solution of phenyacetonitrile **2a** (0.19 g, 1 mmole) and potassium *t*-butoxide (1 g) in dry DMF (8 ml) was added dropwise a solution of 3-chloro-6-phenyl-1,2,4-triazine **1a** in DMF (2 ml) at 0 °C under argon. After stirring at 0 °C for 1 hour, the reaction mixture was poured into ice-water and neutralized with acetic acid. The solvent was evaporated under reduced pressure and the dry residue was extracted with chloroform. The solvent was evaporated and the resulting solid was chromatographed on silica gel and eluted with chloroform to give **3a** as a yellow solid (see Table I, II) and traces of 3-(dimethylamino)-6-phenyl-1,2,4-triazine **4**, mp 115-117 °C. Lit. [17], mp 115-117°.

To a solution of **5** (0.1 g, 0.36 mmole) in acetone (2 ml) was added 15% aqueous ammonium hydroxide (2 g). The resulting mixture was stirred at 50 °C for 1 hour. The solvent was evaporated under reduced pressure and the residue was washed with water. Drying to a constant weight provided **3a** as a yellow solid (Table I, II).

Method b.

3-Amino-4-ethoxycarbonyl-6-phenylpyridazine (**3b**).

To a stirred solution of ethyl cyanoacetate **2b** (0.124 g, 1.1 mmoles) and potassium *t*-butoxide (1 g) in dry DMA (8 ml) was added dropwise a solution of **1a** (0.191 g, 1 mmole) in DMA (2 ml) at 0 °C. After stirring at 0 °C for 1 hour, the reaction mixture was poured into ice-water, neutralized with acetic acid and stored at refrigerator for 24 hours. The resulting crude precipitate was filtered and purified by recrystallization from hexane-chloroform mixture to yield **3b** (see Table I, II).

Anal. Calcd. for $C_{13}H_{13}N_3O_3$ (240.10); C, 64.17; H, 5.39; N, 17.28. Found: C, 63.96; H, 5.20; N, 17.35.

3-Amino-4-cyano-6-phenylpyridazine (**3c**).

Compound **3c** was prepared from **1a** (0.191 g, 1 mmole) and malononitrile **2c** (0.072 g, 1.1 mmoles) as described above. After stirring at 0 °C for 1 hour, the reaction mixture was poured into ice-water and neutralized with acetic acid and evaporated under reduced pressure. The residue was extracted with chloroform. The solvent was evaporated and the crude **3c** was purified by column chromatography (silica gel, chloroform-acetone 10:1) (see Table I, II).

*Anal.*Calcd. for $C_{11}H_8N_4$ (196.07): C, 67.32; H, 4.11; N, 28.57. Found: C, 67.07; H, 4.02; N, 28.28.

3-Amino-6-phenyl-4-(phenylsulfonyl)pyridazine (**3d**).

To a stirred solution of (phenylsulfonyl)acetonitrile **2d** (0.199 g, 1.1 mmoles) and **1a** (0.191 g, 1 mmole) in THF (4 ml) was added potassium *t*-butoxide (0.336 g, 6 mmoles) at -75 °C under argon in a few portions. After stirring at -75 °C for 5 hours, the reaction mixture was quenched with saturated ammonium chloride (1-2 ml). The solvent was evaporated under reduced pressure. The crude **3d** was purified by preparative TLC (silica gel, chloroform-acetone 10:1) followed by recrystallization from ethanol (see Table I, II).

Anal. Calcd. for $C_{16}H_{13}N_3O_2S$ (311.07): C, 61.72; H, 4.21; N, 13.50. Found: C, 61.68; H, 4.19; N, 13.47.

1,2-Diaza-1,5-dicyano-3,4-diphenyl-1,3-pentadiene (**5b**).

To a stirred solution of benzyl cyanide **2a** (0.19 g, 1.1 mmoles) and potassium *t*-butoxide (1 g) in dry DMA (8 ml) was added dropwise a solution of 3-chloro-6-phenyl-1,2,4-triazine **1a** in DMA (2 ml) at 0 °C under argon. After stirring at 0 °C for 1 hour, the reaction mixture was poured into ice-water. The precipitated **5b** was filtered and washed with water. The filtrate was extracted with ether. Removal of the solvent gave an additional amount of **5b**. The combined solids were purified by recrystallization from acetone-water mixture. Total yield of **5b** is 0.27 g, 86%, mp 117-118°; ir (potassium bromide): 3500 (NH), 2260 (CN) cm^{-1}; ^1H nmr (deuteriated acetone): δ 2.81 (br.s, 1H, NH), 7.44-8.24 (m, 11H, aromatic and olefinic protons); hrms, m/z 272.1061. Calcd. for $C_{17}H_{12}N_4$: 272.1062.

5-(1-Cyano-1-phenylmethyl)-2,5-dihydro-3-(methylthio)-6-phenyl-1,2,4-triazine (**6**).

To a stirred solution of phenylacetonitrile **2a** (0.19 g, 1 mmole) and potassium *t*-butoxide (1 g) in dry DMA (4 ml) was added dropwise a solution of 3-(methylthio)-6-phenyl-1,2,4-triazine **1b** (0.191 g, 1 mmole) in DMA (2ml) at 0 °C under argon. After stirring at 0 °C for 4 hours the reaction mixture was poured into ice-water, neutralized with acetic acid, extracted with ether, dried (magnesium sulfate) and evaporated. The crude **6** was purified by column chromatography (silica gel, chloroform), followed by recrystallization from ethanol-water to give **6** (0.16 g, 53%), mp 163 °C; ir (potassium bromide): 3350 (NH), 2250 (CN) cm^{-1}; ^1H nmr (deuteriated chloroform): δ 2.42 (s, 3H), 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, 20H), 7.82 (s, 1H, NH), 8.45 (s, 1H, NH).

Anal. Calcd. for $C_{18}H_{16}N_4S$ (320.12): C, 67.48; H, 5.04; N, 17.50. Found: C, 67.38; H, 5.04; N, 17.41.

[^{15}N]-Phenylacetonitrile (**2a***).

To a mixture of potassium cyanide (1.25 g, 10.7 mmoles) containing 7.0% atom excess of ^{15}N and benzyl bromide (2.73 g, 15.9 mmoles) in water (2.5 ml) the tributylamine (0.018 g, 0.1 mmole) was added. The resulting mixture was heated at 100-105 °C for 3 hours and was then extracted with ether. After evaporation of the solvent from the combined extractions, the remaining residue was distilled at 229-231 °C to yield 1.7 g (91%) of **2a***. The enrichment of ^{15}N in **2a*** amounted to 7.0%.

Conversion of 3-Chloro-6-phenyl-1,2,4-triazine **1a** into 3-[^{15}N]Amino-4,6-diphenylpyridazine (**3a***).

The conversion was carried out by the same procedure as described for the unlabeled compound **3a** (Method a).

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[1] Part 10 in 1,2,4-triazines in organic synthesis. For part 9, see T. Lipiñska, *Khim. Geterotsikl. Soedin.*, (submitted).

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