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1,2,4-TRIAZINE IN ORGANIC SYNTHESIS. 16.* REACTIVITY OF 3-SUBSTITUTED 6-PHENYL-1,2,4-TRIAZINES TOWARDS PHENYLACETONITRILE ANION IN POLAR APROTIC SOLVENTS*[2]

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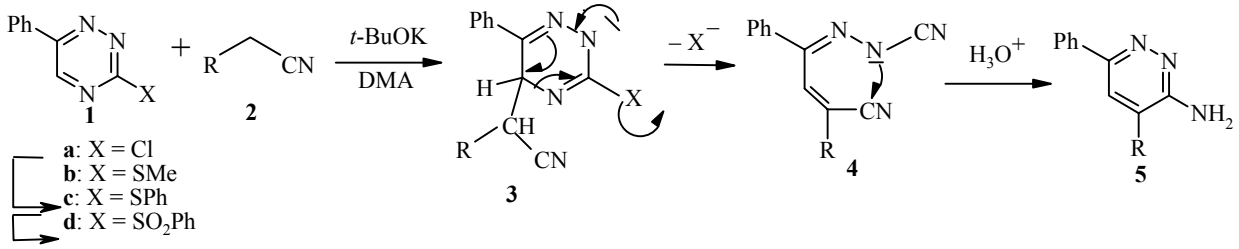
The reactions of 3-X-6-phenyl-1,2,4-triazines (X = SMe, SPh, SO_2Ph) with phenylacetonitrile anion in DMF were studied. In these reactions the ring transformation product 3-amino-4,6-diphenylpyridazine, the covalent addition product 3-X-5-(α-cyanobenzyl)-6-phenyl-2,5-dihydro-1,2,4-triazine, and the ipso-substitution product 3-(1-cyano-1-phenylmethyl)-6-phenyl-1,2,4-triazine were obtained. Analogous reactions carried out in DMA gave only the addition products in excellent yields as diastereomeric mixtures of the corresponding 2,5-dihydro-1,2,4-triazines.

Keywords: 3-substitued 1,2,4-triazines, nucleophilic addition of phenylacetonitrile anion, diastereomeric mixtures of 2,5-dihydrotriazines.

In a previous paper [2] of these series we reported on an ANRORC-type ring transformation of 3-chloro-6-phenyl-1,2,4-triazine (**1a**) with substituted acetonitriles (**2a-d**, R = Ph, CO_2Et, CN, SO_2Ph) (Scheme 1) resulting in the formation of functionalized 3-amino-4-R-6-phenylpyridazines (**5a-d**, R = Ph, CO_2Et, CN, SO_2Ph).

Scheme 1



2, **5 a**: R = Ph, **b**: R = CO_2Et **c**: R = CN, **d**: R = SO_2Ph

* For communication 15, see [1].

*[2] Dedicated to Professor E. Lukevics on the occasion of his 65th birthday.

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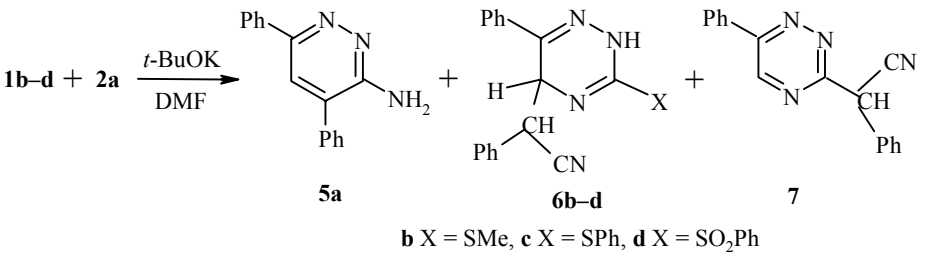
The reaction proceeded with high regioselectivity, involving addition of the nucleophile at C(5) in **1a**, ring opening with breaking of the N(4)–C(5) bond in **3** and an intramolecular ring closure of the resulting open-chain intermediate **4**. By a ^{15}N study with labeled phenylacetonitrile (**2a***) in DMF, it was proved that the ring closure occurs by a nucleophilic attack of the hydrazone nitrogen to the carbon atom of the nitrile reagent. By reacting **1a** in dimethylacetamide (DMA) the reaction stops at the ring opening step and an open-chain compound **4** (R = Ph) could be isolated after neutralization with acetic acid. Treatment of this open-chain compound with aqueous ammonium hydroxide in acetone gives the final aminopyridazine **5a**.

Continuing these investigations we became interested how the course of reaction would be influenced by the presence of substituents at C(3) having a leaving group mobility but other than the chlorine atom. In the present paper we report on the results of reaction of 3-(methylsulfanyl)- (**1b**), 3-(phenylsulfanyl)- (**1c**), and 3-(phenylsulfonyl)-6-phenyl-1,2,4-triazine (**1d**) with phenylacetonitrile (**2a**) in different polar aprotic solvents under basic conditions.

Compound **1b** was prepared by condensation of thiosemicarbazide with isonitrosoacetophenone according to a reported method [3]. Reaction of 3-chloro-6-phenyl-1,2,4-triazine (**1a**) with potassium thiophenolate proceeded smoothly and gave within 30 min at room temperature 6-phenyl-3-(phenylsulfanyl)-1,2,4-triazine (**1c**) in good yield. Oxidation of sulfide **1c** with potassium permanganate under phase-transfer catalysis conditions provided sulfone **1d** respectively (Scheme 1).

Treatment of **1b** with **2a** in DMF in the presence of an excess of potassium *t*-butoxide at 0°C led to a mixture of three products: the ring transformation product, 3-amino-4,6-diphenylpyridazine (**5a**) (11%), the covalent addition product, 5-(α-cyanobenzyl)-2,5-dihydro-3-(methylsulfanyl)-6-phenyl-1,2,4-triazine (**6b**) (20%), and the *ipso* substitution product, 3-(α-cyanobenzyl)-6-phenyl-1,2,4-triazine (**7**) (23%) (Scheme 2).

Scheme 2



b X = SMe, **c** X = SPh, **d** X = SO_2Ph

Products **5a** and **6b** are known compounds and were already described in a previous paper [2]. The structure assignment of **7** is based on its micro analysis, its mass spectrum clearly showing the highly delocalized phenylacetylene radical ion at 102 (100%) mass units, and on its IR spectrum featuring the presence of the cyano group (2250 cm^{-1}). In the ^1H NMR spectrum a singlet for the methine hydrogen is observed at $\delta = 5.10$. Applying the same conditions, compound **1c** gave with **2a** a mixture of **5a** (30%), **6c** (22%), and **7** (37%); compound **1d** gave about a similar mixture of products, i.e., **5a** (16%), **6d** (51%), and **7** (16%).

The covalent addition products **6b-d** are obtained as diastereomeric mixtures of the corresponding 2,5-dihydro-1,2,4-triazines [4]. The ^1H NMR spectra of **6b-d** are given in Table 1 together with those for 2,5-dihydro-1,2,4-triazine (**8**).

Compound **8** was prepared by the reaction of **1c** with 2-phenylpropionitrile **2e** in liquid ammonia containing 2 equivalents of sodium amide at -75°C. These low-temperature conditions are necessary in order to avoid oxidation of 2-phenylpropionitrile anion into acetophenone anion [5], since the latter compound easily undergoes covalent addition at C(5) of **1c** to yield compound **9** (Scheme 3).

TABLE 1. ^{1}H NMR Data of Compounds **1b-c**, **6b-d** and **8** for Two Diastereomers

Com-pound	Solvent	^{1}H NMR, δ, ppm, *J* (Hz) [Δδ]*			
		Methine C–H	5-H	Ph	N–H
1b[*2]	$CDCl_3$	—	9.50 (s, 1H)	7.30-7.75	—
6b[*3]	$CDCl_3$	4.04 (d, 1H, *J* = 8.71)	5.24 (d, 1H, *J* = 5.72) [4.26]	7.07-7.44	7.82 (s, 1H) 8.45 (s, 1H)
		4.12 (d, 1H, *J* = 8.68)	5.49 (d, 1H, *J* = 5.72) [4.01]	—	—
1c	$CDCl_3$	—	8.80 (s, 1H)	7.40-7.90	—
6c	DMSO-d_6	4.27 (d, 1H, *J* = 7.26)	5.32 (d, 1H, *J* = 7.3) [3.48]	7.12-7.87	11.22 (s, 1H) 11.6 (s, 1H)
		4.30 (d, 1H, *J* = 7.26)	5.51 (d, 1H, *J* = 7.3) [3.29]	—	
1d	DMSO-d_6	—	9.62 (s, 1H)	7.36-8.26	—
6d	DMSO-d_6	4.37 (d, 1H, *J* = 5.98)	5.56 (d, 1H, *J* = 6.03) [4.05]	7.07-8.33	11.99 (s, 1H) 12.58 (s, 1H)
		4.50 (d, 1H, *J* = 5.51)	5.78 (d, 1H, *J* = 5.29) [3.84]		
1c	$CDCl_3$	—	8.80 (s, 1H)	7.40-7.90	—
8[*4]	DMSO-d_6	—	5.34 (s, 1H) [3.46] 5.48 (s, 1H) [3.32]	7.18-7.74	11.10 (s, 1H) 11.28 (s, 1H)

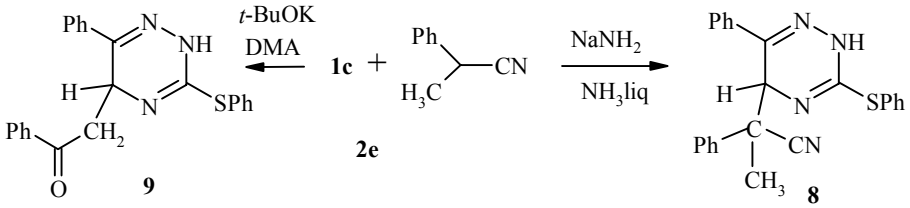
* $\Delta\delta = \delta_{\mathbf{1b\text{-}d}} - \delta_{\mathbf{6b\text{-}d}\text{ or }\mathbf{8}}$.

*[2] Other signal: 2.55 (s, 3H, Me).

*[3] Other signals: 2.42 (s, 3H, Me), 2.61 (s, 3H, Me).

*[4] Other signals: 1.54 (s, 3H, Me), 1.60 (s, 3H, Me).

Scheme 3



Measurements of the ^{1}H NMR spectra of **6b-d** and **8** in $CDCl_3$ or DMSO-d_6 at room temperature showed that diastereomeric H(5) protons in these compounds appeared at a much higer field than the resonance signals observed in the solution of compounds **1b-d** in $CDCl_3$ (Table 1). The magnitudes of the upfield shifts Δδ are very close to those found in σ-amino adducts [6]. The general view of the ^{1}H NMR data of these 2,5-dihydro-1,2,4-triazines (**6b-d**) discloses that: (i) the replacement of the 3-methylsulfanyl by phenylsulfanyl group only exerts a slight effect on H(5), but a significant effect on N<u>H</u> within each pair of diastereomers; (ii) the chemical shifts of H(5) protons in **6b-d** are nearly the same as that of the analogous proton in **8**.

The structure assignments of 2,5-dihydro-1,2,4-triazines (**6b-d**) were confirmed by measuring their ^{13}C NMR spectra under conditions as mentioned before. As expected, all carbon atoms are shifted upfield compared with the shieldings of the corresponding carbon atoms of compounds **1b-d** in $CDCl_3$. The greater upfield shift found for C(5) proves the formation of the covalent adduct **6** (Table 2).

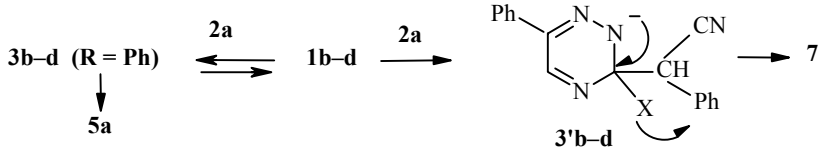
TABLE 2. ^{13}C NMR Data of Compounds **1b-d** and **6b-d**

Compound	Solvent	^{13}C NMR, δ, ppm [Δδ]*					
		C(5)	C(6)	C(3)	CN	Methine C	Ph
1b*[2]	$CDCl_3$	152.98	145.97	172.00	—	—	126.19, 129.20 130.49, 132.95
6b*[3]	$CDCl_3$	57.58 [95.40]	143.37 [2.60]	157.36 [14.64]	118.74	38.52	125.83, 128.08 128.45, 128.60 128.81, 129.35 131.79, 133.63
1c	DMSO-d_6	153.46	147.85	171.28	—	—	126.42, 127.31 129.15, 129.59 129.80, 130.65 132.75, 135.22
6c	DMSO-d_6	56.23 [97.23]	141.17 [6.68]	154.87 [16.41]	119.47	38.33	125.56, 127.93 128.17, 128.32 128.65, 128.90 128.99, 129.06 132.58, 133.91 134.54, 134.61
1d	DMSO-d_6	157.87	149.97	165.55	—	—	127.85, 129.25 129.36, 129.74 131.90, 132.05 135.10, 136.77
6d	DMSO-d_6	55.84 [102.03]	140.68 [9.29]	154.57 [10.98]	118.75	40.58	126.03, 128.15 128.42, 128.48 128.62, 128.99 129.62, 129.92 131.80, 132.97 135.10, 136.64

* $\Delta\delta = \delta_{\mathbf{1b\text{-}d}} - \delta_{\mathbf{6b\text{-}d}}$.
*[2] Other signal: 13.88, Me.
*[3] Other signal: 14.02, Me.

The results of reaction **1b-d** with **2a** show a lower regioselectivity than reported earlier for **1a** [2], although from the yields of the products, **5a** and **6b-d** it is clear that the C(5) position in compounds **1b-d** is still the preferential site of nucleophilic attack. The low percentage of ring transformation product **5a** and the presence of an *ipso* substitution product **7** require some comments in terms of the leaving group mobility. As we have seen before [2] the reaction of **2a** with **1a** proceeds *via* adduct **3**, followed by ring opening; no traces of product **7** were isolated, although the chlorine atom is considered to be a better leaving group than the sulfur-containing groups when located at C(3) of the 1,2,4-triazine ring [7]. Since in this study we deal with compounds **1b-d** that do not contain a good leaving group at C(3), the driving force for bond breaking of the intermediary **6b-d** is diminished. The σ^{H}-adducts **3b-d** partly isomerize to the σ^{SR}-, σ^{SPh}-, and σ^{SO2Ph}-adducts **3'b-d,** respectively, *via* **1b-d**. Departure of the leaving group from the latter adducts easily occurs, resulting in the formation of product **7** (Scheme 4).

Scheme 4



During preliminary exploration of the conditions for reaction of **1b** with **2a** we used DMA instead of DMF as reaction medium. Under these conditions a stable 2,5-dihydro-1,2,4-triazine **6b** was exclusively formed after neutralization, as a mixture of two diastereomers [2]. Neither compound **5a** nor **7** were obtained. Selective preference of **6b** over **5a** and **7** in this solvent was also found with the compounds **1c** and **1d.** Reaction with **2a** in DMA gave, after neutralization, a mixture of diastereomeric 2,5-dihydro-1,2,4-triazines (**6c**) and **6d** respectively. The latter result indicates that even the highly reactive phenylsulfonyl group is drastically deactivated towards nucleophilic substitution when the reaction is carried out in DMA. This unusual solvent effect requires further studies.

EXPERIMENTAL

General Methods. Melting points were determined on a Boethius melting point aparatus and were uncorrected. NMR spectra were recorded on Varian Gemini (200 MHz) with TMS as internal standard. Mass spectra were obtained with AMD 604 Inectra spectrometer. Reactions were monitored by TLC using precoated silica gel aluminium plates containing a fluorescent indicator. Detection was done by exposure to UV light (254 nm).

Synthesis of 6-Phenyl-3-phenylsulfanyl-1,2,4-triazine (1c). To a stirred solution of KOH (0.233 g, 4 mmol) in anhydrous ethanol (5 ml) a solution of thiophenol (0.480 g, 4 mmol) in anhydrous ethanol (5 ml) was added. The mixture was cooled in an ice-water bath to 0°C and 3-chloro-6-phenyl-1,2,4-triazine **1a** (0.764 g, 4 mmol) was added in one portion. After stirring at room temperature for 30 min, the precipitate was filtered off and washed with chloroform. The combined extracts were evaporated under reduced presure and the residue was recrystallized from ethanol to give **1c** as a yellow needles. Yield 0.960 g (86 %); mp 95-97°C. Found, %: C 68.12; H 4.13; N 15.78. $C_{15}H_{11}O_3S$. Calculated, %: C 67.92; H 4.15; N 15.85.

Synthesis of 6-Phenyl-3-phenylsulfonyl-1,2,4-triazine (1d). To a solution of potassium permanganate (1.050 g, 7 mmol) in water (25 ml) a solution of **1c** (0.265 g, 1 mmol) in benzene (23 ml), tetrabutylammonium bromide (45 mg), and acetic acid (3 ml) was added. The mixture was stirred at room temperature for 2 h. Then the mixture was cooled in an ice-water bath and sodium pyrosulfite was added to remove manganese(IV) oxide. The mixture was neutralized with potassium carbonate and the benzene layer was separated. The water phase was extracted twice with benzene (30 ml). The benzene extracts were combined and dried with magnesium sulfate. The solvent was evaporated under reduced pressure to give **1d**. The product was purified by column chromatography using chloroform–acetone (50:1) as eluent. Yield 0.155 g (69 %); mp 218-219°C. IR spectrum (KBr), ν, cm^{-1}: 1336, 1141 (SO_2). Found, %: C 59.61; H 3.83; N 13.84. $C_{15}H_{11}N_3O_2S \cdot 1/3H_2O$. Calculated, %: C 59.41; H 3.85; N 13.86.

Reactions of 1b-d with 2a in DMA. To a stirred solution of phenylacetonitrile **2a** (0.190 g, 1 mmol) and potassium *t*-butoxide (1 g) in dry DMA (4 ml) a solution of compounds **1b, 1c**, or **1d** (1 mmol) in DMA (4 ml) was added dropwise at 0°C under argon. After stirring at 0°C for 4 h the reaction mixture was poured into ice-water and neutralized with acetic acid. The precipitate was filtered off and washed with water. The product was purified by column chromatography using chloroform as eluent, followed by recrystallization from ethanol.

5-(1-Cyano-1-phenylmethyl)-3-(methylsulfanyl)-6-phenyl-2,5-dihydro-1,2,4-triazine (6b). Yield 0.160 g (53 %); mp 163°C. IR spectrum (KBr), ν, cm^{-1}: 3350 (NH), 2250 (CN). Found, %: C 67.38; H 5.04; N 17.41. $C_{18}H_{16}N_4S$. Calculated, %: C 67.48; H 5.04; N 17.50.

5-(1-Cyano-1-phenylmethyl)-6-phenyl-3-(phenylsulfanyl)-2,5-dihydro-1,2,4-triazine (6c). Yield 0.186 g (85 %); mp 189-190°C. IR spectrum (KBr), ν, cm^{-1}: 3480 (NH), 2260 (CN). Found, %: C 72.27; H 4.68; N 14.50. $C_{23}H_{18}N_4S$. Calculated, %: C 72.25; H 4.71; N 14.65.

5-(1-Cyano-1-phenylmethyl)-6-phenyl-3-(phenylsulfonyl)-2,5-dihydro-1,2,4-triazine (6d). Yield 0.132 g (63 %); mp 194-196 °C. IR spectrum (KBr), ν, cm^{-1}: 3450 (NH), 1350, 1160 (SO_2Ph). HRMS LSIMS found: 415.12269. $C_{23}H_{19}N_4O_2S$. Calculated 415.12287.

Reactions of 1b-d with 2a in DMF. To a stirred solution of phenylacetonitrile **2a** (0.190 g, 1 mmol) and potassium *t*-butoxide (1 g) in dry DMF (4 ml) was added dropwise a solution of compounds **1b, 1c**, or **1d** (1 mmol) in DMF (4 ml) at 0°C under argon. After stirring at 0°C for 4 h the reaction mixture was poured into ice-water and neutralized with acetic acid. The precipitate was filtered off and washed with water. The products were separated by preparative TLC using chloroform–acetone (50:1) as eluent. For yields of compounds **5a, 6b-d** and **7** see the main text.

3-(1-Cyano-1-phenylmethyl)-6-phenyl-1,2,4-triazine (7). Mp 160-161°C. IR spectrum (KBr), ν, cm^{-1}: 2250 (CN). ^1H NMR ($CDCl_3$): 5.74 (s, 1H, CH); 7.31-7.64 (m, 9H, Ph and H_{Het}); 8.02-8.11 (m, 2H, Ph). Found, %: C 74.97; H 4.47; N 20.39. $C_{17}H_{12}N_4$. Calculated, %: C 75.00; H 4.41; N 20.60.

Reaction of 1c with 2-Phenylpropionitrile (2e) and $NaNH_2$ in NH_3-liq. 2-Phenylpropionitrile (**2e**) (0.269 g, 2 mmol) was added dropwise to a suspension of freshly prepared sodium amide (2 mmol) in liquid ammonia (25 ml) at -75°C. After 1 min **1c** (0.265 g, 1 mmol) dissolved in DMF (1 ml) was added dropwise at such a rate that the temperature did not exceed -75°C. The reaction mixture was stirred for 2 min and quenched with solid ammonium chloride (1.1 g, 20 mmol), and ammonia was evaporated. 5-(1-Cyano-1-phenylethyl)-6-phenyl-3-phenylsulfanyl-2,5-dihydro-1,2,4-triazine (**8)** was isolated by extraction with chloroform and purified by column chromatography (silica gel, hexane–ethyl acetate, 10:1) and recrystallized from ethanol. Yield 0.174 g (44%); mp 89-90°C. IR spectrum (KBr), ν, cm^{-1}: 2235 (CN), 3411 (NH), HRMS LSIMS found: 397.14876. $C_{24}H_{21}N_4S$. Calculated 397.14868.

Reaction of 1c with 2-Phenylpropionitrile in DMA. To a stirred solution of 2-phenylpropionitrile (**2e**) (0.131 g, 1 mmol) and potassium *t*-butoxide (1 g) in dry DMA (4 ml) was added dropwise a solution of **1c** (265 mg, 1 mmol) in DMA (4 ml) at 0°C under argon. After stirring at 0°C for 1 h the reaction mixture was poured into ice-water and neutralized with acetic acid. The precipitate was filtered off and washed with water. 5-Phenacyl-6-phenyl-3-phenylsulfanyl-2,5-dihydro-1,2,4-triazine (**9**) was purified by column chromatography (silica gel, hexane–ethyl acetate 10:1) followed by recrystallization from ethanol. Yield 0.103 g (26%); mp 153-154°C. IR spectrum (KBr), ν, cm^{-1}: 1684 (CN), 3401 (NH). ^1H NMR ($CDCl_3$): 2.99 (dd, 1H, J = 15.6, 4.6 Hz, $H_AC\underline{H}_B$); 3.41 (dd, 1H, J = 15.6, 8.5 Hz, $\underline{H}_ACH_B$); 5.57 (dd, 1H, J = 8.5, 4.6 Hz, 5-H); 7.35-7.58 (m, 11H, Ph); 7.71-7.75 (m, 2H, Ph); 7.86-7.89 (m, 2H, Ph). Found, %: C 71.77; H 4.72; N 10.98. $C_{23}H_{19}N_3OS$. Calculated, %: C 71.69; H 4.93; N 10.90.

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