LITHIATION OF 3-ARYL-1,2,4,5-TETRAZINES

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Abstract: 3-Aryl-1,2,4,5-tetrazines **1a-d** were lithiated with lithium 2,2,6,6-tetramethylpiperidide and the formed lithio-1,2,4,5-tetrazines trapped with aldehydes or benzophenone to give 3-aryl-6-(α-hydroxymethyl)-1,2,4,5-tetrazines **2a-h**. Side-products of these reactions are 3-aryl-6-(2,2,6,6-tetramethylpiperidyl-1)-1,2,4,5-tetrazines **3a, c, d** and 1-aryl-4-(6-aryl-1,2,4,5-tetrazinyl-3)-2,3-diazabutadienes **4a-d**.

Introduction

Lithio-substituted heterocycles are versatile intermediates in the synthesis of complex heterocyclic compounds (1-4). Lithiopyridines (2, 4-9), lithiopyridazines (2-4, 10-12), lithiopyrimidines (2-4, 6, 7, 10, 13-19), lithiopyrazines (2-4, 20), lithio-1,2,3-triazines (21), and lithio-1,2,4-triazines (22-24) are known.

In general *o*-directed metalation reaction, which involves deprotonation by a strong base in the *ortho*-position with respect to a direction group containing a heteroatom, was used for the lithiation of the mentioned heterocycles. Lithiation of heterocycles without an *ortho*-directing group is reported in a few cases (19, 25, 26).

Due to its structure *o*-directed metalation of 1,2,4,5-tetrazines is not possible. Therefore we studied whether the lithiation of 3-aryl-1,2,4,5-tetrazines can be achieved or not.

Results and Discussion

Two methods for the lithiation of electrondeficient heterocycles are known: the accumulation method and the equilibrium shift method. In the first case, the base is added to the educt and after accumulation of the lithio compound the electrophile is added. In the other case the base is added to a mixture of the educt and the electrophile. This method can only be used in those cases where the base does not react with the electrophile.

Due to our results in the lithiation of 3-phenyl-1,2,4,5-tetrazine **1a** with lithium 2,2,6,6-tetramethylpiperidide (LiTMP) and reaction of the lithio-1,2,4,5-tetrazine with benzaldehyde the equilibrium

shift method gives better yields of the desired reaction product than the method of accumulation. The ratio educt to base should be 1:4 or 1:6, then the yield of product **2a** is between 20 and 26 %. (Table 1)

Beside **2a** we isolated two additional products, the 3-phenyl-6-(2,2,6,6-tetramethylpiperidyl-1)-1,2,4,5-tetrazine **3a** and the 1-phenyl-4-(6-phenyl-1,2,4,5-tetrazinyl-3)-2,3-diazabutadiene **4a**.

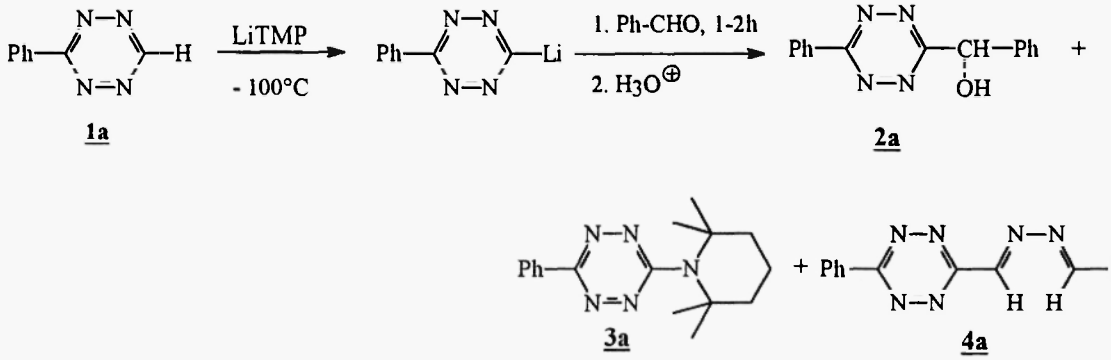
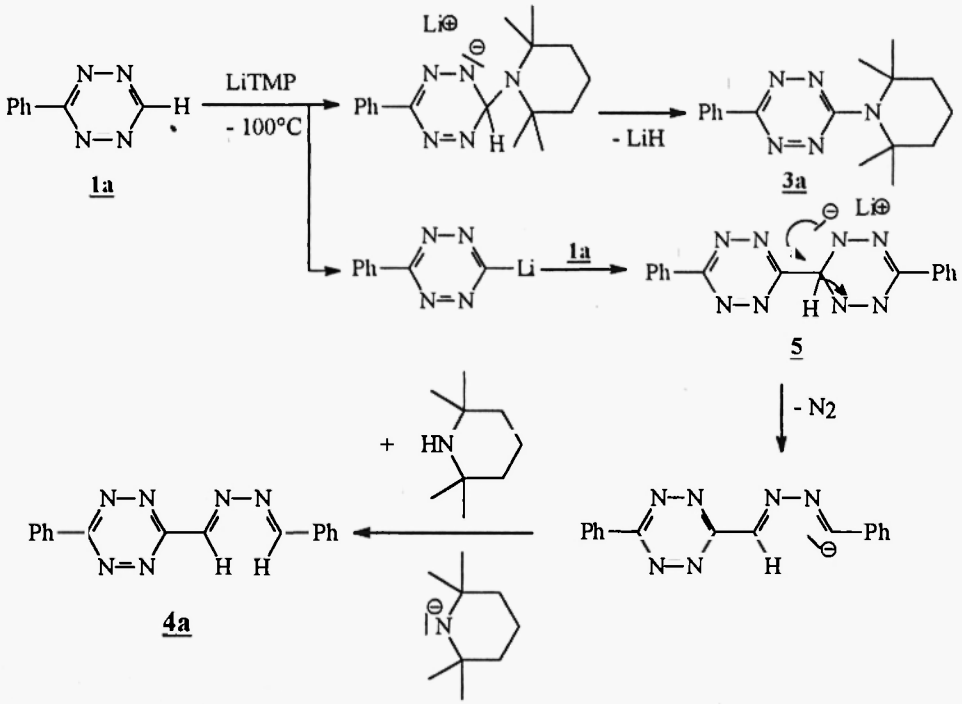


Table 1: Influence of the ratio tetrazine/base and time of accumulation on the yield of **2**

ratio **1a**/ base	accum. time (min)	react. time (h)	yield [%] **2a**	**3a**	**4a**	**1a**
1 : 2	3	2	0	3	4	-
1 : 2	10	1	6	10	4	18
1 : 2	20	1	0	4	4	13
1 : 4	0 (equil)	1	20	3	4	23
1 : 4	5	1	6	15	3	25
1 : 4	10	1	10	8	3	16
1 : 4	15	1	0	3	3	21
1 : 6	0 (equil)	1	26	5	3	19
1 : 6	0 (equil)	2	17	6	3	21
1 : 6	10	1	1	9	3	23
1 : 8	0 (equil)	1	19	3	3	19

The formation of **3a** can be explained by a nucleophilic addition of the base to the 1,2,4,5-tetrazine, followed by elimination of LiH (Chichibabin-like reaction). For the formation of **4a** we suggest the following mechanism: the lithio-1,2,4,5-tetrazine adds to the starting 1,2,4,5-tetrazine leading to **5**, ring opening with elimination of nitrogen affords **4a**.



Variation of the 3-aryl group in the 1,2,4,5-tetrazine **1b-d** has only a small influence on the yield of **2b-d**. Only in the case of **1d** the yield of **2d** is smaller, in return the yield of **4d** is higher (Table 2).

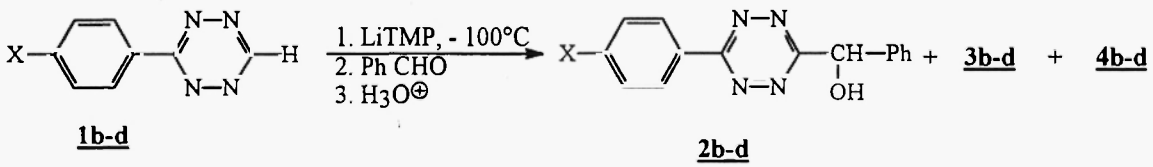
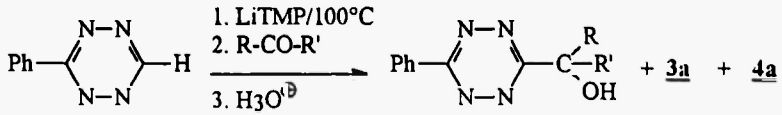


Table 2: Influence of the Aryl-substituent in **1** on the yield of **2**

			yield [%]			
1	X	ratio **1**/base	**2**	**3**	**4**	**1**
b	Cl	1 : 4	16	4	0	12
b	Cl	1 : 6	20	4	0	8
c	CH_3O	1 : 4	12	4	3	32
c	CH_3O	1 : 6	19	3	6	31
d	CH_3	1 : 4	7	5	16	26
d	CH_3	1 : 6	15	4	8	27

The yield of the expected product depends much more on the electrophile used. With acetaldehyde or benzophenone the yield of **2g** and **2h** is only 9 and 10 %, respectively, while with benzaldehyde, 4-bromobenzaldehyde or 4-tolylaldehyde yield between 25 and 30 % were obtained. (Table 3)



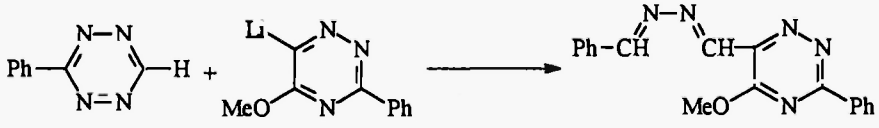
1a **2e-h**

Table 3: Variation of the electrophile

	R	R'	ratio **1a**/base	yield [%] **2**	**3a**	**4a**	**1a**
e	4-BrC_6H_4	H	1 : 6	30	2	7	41
f	4$CH_3C_6H_4$	H	1 : 6	25	2	10	24
g	CH_3	H	1 : 6	9	11	1	6
h	Ph	Ph	1 : 4	8	15	4	7
h	Ph	Ph	1 : 6	10	17	5	5

Lithiation of the 1,2,4,5-tetrazines **1a,b** and addition of chlorotrimethylsilane to the lithio-1,2,4,5-tetrazines afforded only the 3-aryl-6-(2,2,6,6-tetramethylpiperidyl-3)-1,2,4,5-tetrazines **3a, b**.

Reaction of 6-Lithio-5-methoxy-3-phenyl-1,2,4-triazine **6** with **1a** led to the isolation of 5-methoxy-3-phenyl-6-(4-phenyl-2,3-diaza-butadien-1,3-yl-1)-1,2,4-triazine **7** which structure was proven by X-ray crystallographic analysis [27].



1a **6** **7**

Table 4: Melting points and elemental analysis of the 1,2,4,5-tetrazines **2a**- **h**, **3a** **d** and **4a**- **d**

No.	M.p. [°C]	Formula Mol mass	Analysis Calculated Found C	H	N
2a	114-115	$C_{15}H_{12}N_4O$	68.16	4.57	21.19
		(264.3)	68.09	4.53	20.97
2b	189-190	$C_{15}H_{11}ClN_4O$	60.31	3.71	18.75
		(298.7)	60.27	3.68	18.49
2c	168-170	$C_{16}H_{14}N_4O_2$	65.28	4.79	19.05
	(ethanol)	(294.3)	65.08	4.74	18.92
2d	154-156	$C_{16}H_{14}N_4O$	69.05	5.07	20.13
	(ethanol)	(278.3)	69.01	4.98	19.99
2e	132-133	$C_{15}H_{11}BrN_4O$	52.50	3.23	16.32
	(ethanol)	(343.2)	52.22	2.99	16.05
2f	110-111	$C_{16}H_{14}N_4O$	69.05	5.07	20.13
		(278.3)	68.98	5.01	19.97
2g	82- 83	$C_{10}H_{10}N_4O$	59.39	4.98	27.71
	(ethanol)	(202.2)	59.36	4.91	27.57
2h	118-120	$C_{21}H_{16}N_4O$	74.10	4.74	16.46
		(340.4)	74.07	4.71	16.31
3a	55- 57	$C_{17}H_{23}N_5$	68.65	7.79	23.55
		(297.4)	68.53	7.72	23.37
3b	97- 99	$C_{17}H_{22}ClN_5$	61.53	6.68	21.10
		(331.9)	61.32	6.62	21.05
3c	98-100	$C_{18}H_{25}N_5O$	66.02	7.69	21.39
		(327.4)	66.04	7.63	21.29
3d	118-120	$C_{18}H_{25}N_5$	69.42	8.09	22.70
		(311.4)	69.39	7.98	22.58
4a	148-150	$C_{16}H_{12}N_6$	66.65	4.19	29.51
		(288.3)	66.63	4.15	28.96
4c	181-182	$C_{18}H_{16}N_6O_2$	62.06	4.63	24.12
	(ethanol)	(348.4)	61.97	4.57	24.08
4d	167-170	$C_{18}H_{16}N_6$	68.33	5.10	26.56
	(ethanol)	(316.4)	68.23	5.02	26.44
7	165-167	$C_{18}H_{15}N_5O$	68.13	4.76	22.07
	(ethanol)	(317.3)	67.99	4.88	21.98

Table 5: Selected spectroscopic data of the 1,2,4,5-tetrazines **2a-h, 3a-d, 4a-d**

No.	^{1}H-NMR data ($CDCl_3$) 300 MHz, δ values	MS: m/z (%) (70 eV)
2a	3.96 (d, *J*=7.0 Hz, 1H); 6.37 (d, *J*=7.0 Hz, 1H); 7.22-7.36, 7.49-7.60 (m, 8H); 8.50 (d, *J*=8 Hz, 2H)	264 (13) [M^+], 103 (100)
2b	6.30 (d, *J*=5.1 Hz, 1H); 6.76 (d, *J*=5.1 Hz, 1H); 7.28-7.40 (m, 3H); 7.56 (d, 2H, *J*=7.2 Hz); 7.75 (d, *J*=9.5 Hz, 2H);8.48 (d, *J*=9.5 Hz, 2H)	299 (4) [M^+, ^{37}Cl], 297 (12) [M^+, ^{35}Cl], 135 (100)
2c	3.85 (s, 3H); 3.93 (d, *J*=6.9 Hz, 1H); 6.33 (d, *J*=6.9 Hz, 1H); 7.01 (d, *J*=9.0 Hz, 2H);7.22-7.35 (m, 3H); 7.52 (d, *J*=7.1 Hz, 2H); 8.48 (d, *J*=9.0 Hz, 2H)	294 (8) [M^+], 133 (100)
2d	2.46 (s, 3H); 4.02 (d, *J*=6.9 Hz, 1H); 6.41 (d, *J*=6.9 Hz, 1H); 7.29-8.48 (m, 9H)	278 (12) [M^+], 117 (100)
2e	4.07 (d, *J*=6.5 Hz, 1H); 6.39 (d, *J*=6.5 Hz, 1H); 7.46-7.68 m, 7H); 8.58 (d, *J*=8.0 Hz, 2H)	344 (7) [M^+, ^{81}Br], 342 (7) [M^+, ^{79}Br], 103 (100)
2f	2.26 (s, 3H); 3.86 (d, *J*=7.0 Hz, 1H); 6.33 (d, *J*=7.0 Hz, 1H) 7.12 (d, *J*=7.8 Hz, 2H); 7.39 (d, *J*=7.8 Hz, 2H); 7.49-7.57 (m, 3H); 8.51 (d, *J*=7.7 Hz, 2H)	278 (27) [M^+], 103 (100)
2g	1.75 (d, *J*=6.5 Hz, 3H); 3.30 (d, *J*=6.5 Hz, 1H); 5.42 (q, *J*=6.5 Hz, 1H);7.53-7.61 (m, 3H); 8.55 (d, 2H, *J*=8.5 Hz)	202 (2) [M^+], 104 (100)
2h	5.05 (s, 1H); 7.23-7.79 (m, 13H); 8.55 (d, *J*=8.0 Hz, 2H)	340 (46) [M^+], 78 (100)
3a	1.61 (s, 12H); 1.89-1.97 (m, 6H); 7.49-7.53 (m, 3H); 8.43 (d, *J*=7 Hz, 2H)	297 (6) [M^+], 151 (100)
3b	1.60 (s, 12H); 1.89-1.98 (m, 6H), 7.49 (d, *J*=8 Hz, 2H) 8.37 (d, *J*=8 Hz, 2H)	333 (3) [M^+, ^{37}Cl], 331 (3) [M^+, ^{35}Cl], 151 (100)
3c	1.51 (s, 12H); 1.84-1.89 (m, 6H); 3.82 (s, 3H); 6.96 (d, *J*=9.0 Hz, 2H); 8.32 (d, *J*=9.0 Hz, 2H)	327 (8) [M^+], 151 (100)
3d	1.53 (s, 12H); 1.78-1.88 (m, 6H); 2.36 (s, 3H); 7.26 (d, *J*=8.1 Hz, 2H);8.25 (d, *J*=8.1 Hz, 2H)	311 (3) [M^+], 151 (100)
4a	7.42-7.47 (m, 3H); 7.55-7.60 (m, 3H); 7.87 (d, *J*=8.0 Hz, 2H); 8.64 (d, *J*=8.0 Hz, 2H); 8.81 (s, 1H); 9.03 (s, 1H)	288 (8) [M^+], 102 (100)
4c	3.83 (s, 3H); 3.88 (s, 3H); 6.94 (d, *J*=8.8 Hz, 2H); 7.05 (d, *J*=9.0 Hz, 2H); 7.82(d, *J*=8.8 Hz, 2H); 8.59(d, *J*=9.0 Hz, 2H); 8.79 (s, 1H), 8.99 (s, 1H)	348 (37) [M^+], 278 (100)
4d	2.44 (s, 3H); 2.49 (s, 3H); 7.31 (d, *J*=8.0 Hz, 2H); 7.42 (d, *J*=8.2 Hz, 2H); 7.82 (d, *J*=8.0 Hz, 2H); 8.58 (d, *J*=8.2 Hz, 2H); 8.86 (s, 1H), 9.07 (s, 1H)	316 (8) [M^+], 117 (100)
7	4.22 (s, 3H); 7.34-7.51 (m, 6H), 7.82 (d, *J*=7.7 Hz, 2H); 8.52 (d, *J*=7.7 Hz, 2H); 8.69 (s, 1H); 8.95 (s, 1H)	53 (100)

Experimental

All manipulations were carried out under argon. - THF was dried with a benzophenone-sodium mixture and distilled directly before use. - Melting points were determined with a melting point microscope (Fa. C. Reichert) and are uncorrected. - ^{1}H-NMR spectra were recorded with a Bruker WM 300 instrument with tetramethylsilane as internal standard. - Mass spectra were recorded with a Varian 311 A with data system Tecnivent 100. - For column chromatography (CC) silica gel (0.063-0.2 mm; Fa. Macherey-Nagel) was used.

Lithiation of 3-aryl-1,2,4,5-tetrazines **1a-d** *and reaction with aldehydes and benzophenone - Synthesis of 3-aryl-6-(α-hydroxymethyl)-1,2,4,5-tetrazines* **2a-h**: To a solution of *n*-BuLi (12 mmol in *n*-hexane) in THF (50 ml) 2,2,6,6-tetramethylpiperidine (2.4 ml, 14 mmol) was added at -30 °C. The solution was warmed to 0 °C and stirred for 30 min. After cooling to -100 °C **1a-d** (2 or 3 mmol) in absol. THF (14/21 ml) and the electrophile (12 or 18 mmol) in absol. THF (10/20 ml) were added simultaneously by two syringes, keeping the temperature below -95 °C. The mixture was stirred for 1 h at -100 °C, then a mixture of conc. hydrochloric acid (3.0 ml), methanol (4.0 ml) and THF (16 ml) was added and the solution warmed slowly to room temp. A saturated sodium hydrogen carbonate solution was added (until pH = 8), the organic solvents were removed under reduced pressure and the aqueous solution extracted with dichloromethane (3 x 40 ml). The combined organic phases were dried with magnesium sulfate, the solvent removed and the residue separated by CC (dichloromethane). Results and physical data are listed in tables 1-5.

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