AMINATIONS WITH OXAZIRIDINES - SYNTHESES OF ARYL- AND HETARYL-HYDRAZINES

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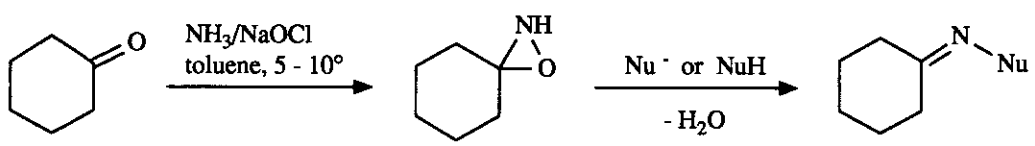
Dedicated to Prof. Dr. A. R. Katritzky on the occasion of his 65th birthday.

Abstract- Five acetylaminobenzenes (**2**) (X= CH), two 3-acetylaminopyridines (**2**) (X= N) and one 3-acetylaminopyridine1-oxide (**2**) (X= N(O)) are aminated by 1-oxa-2-azaspiro[2.5]octane (**1**) / DABCO to cyclohexylidenehydrazino compounds (**3**), which are characterized as benzaldehyde or 4-nitrobenzaldehydehydrazones (**4**). In some cases the acetyl group is removed during the amination.

Among NH-transfer reagents 1-oxa-2-azaspiro[2.5]octane (**1**, 3,3-pentamethyleneoxaziridine) plays an important role.[1] Its reactivity is somewhat less than that of the well known *O*-substituted hydroxylamine derivatives, e.g. hydroxylamine-*O*-sulfonic[2] acid or *O*-mesitylsulfonylhydroxylamine.[3] As a rule, only the latter attack nitrogen of an aromatic ring or a tertiary amine. The oxaziridine (**1**) is distinguished by its simple accessibility: Solutions of (**1**) are obtained within one minute from cyclohexanone, ammonia and



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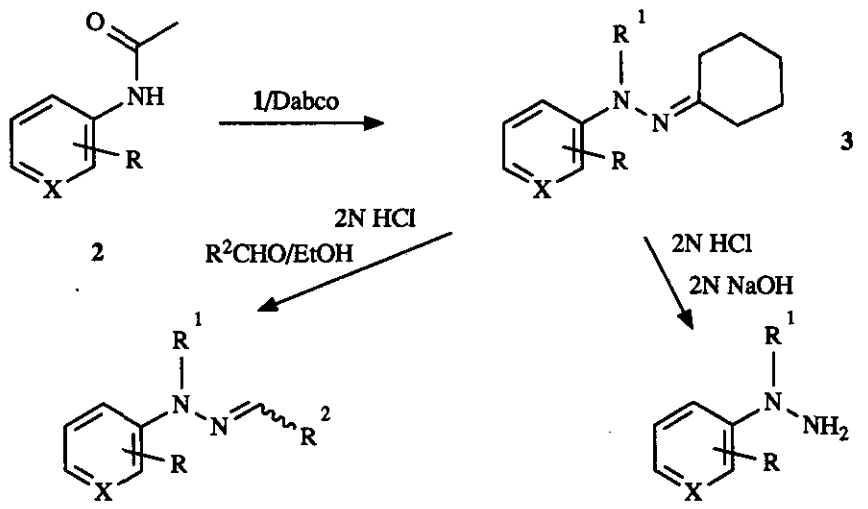
Nu - = nucleophile (>N -, -O -, -S -, >CH -)

hypochlorite solutions.[4] A special advantage of **1** in N-N-forming reactions is the protection of the primary

products by the cyclohexylidene system against a further attack of the aminating reagent. Probably, overamination is one reason why deprotonated *N*-tosylaniline on amination with *O*-mesitylsulfonylhydroxylamine gave *N*-tosylphenylhydrazine only in a yield of 25 %.[5] Aliphatic, preferably secondary amines are converted to hydrazine derivatives by the oxaziridine (**1**) in fair to excellent yields.[1] However, our early attempts to aminate aromatic amines completely failed and only 3-ethyl-3-methyloxaziridine aminated aniline to phenylhydrazine in 22 % yield (isolated as the benzaldehyde hydrazone).[6]

We expected that the increased nucleophilicity of deprotonated acylamines would enable them to be aminated more efficiently. In fact, we observed an exothermic reaction of acylaminoarenes with the oxaziridine (**1**) in the presence of a tertiary organic base and obtained arylhydrazine derivatives in good yield. Depending on the reactivity of the acylaminoarene in some cases much less than one equivalent of the base (0.09 - 1.4 mol DABCO per mol **2**) can effect a nearly complete conversion of the starting material. Thus, on addition of 0.18 equivalents of DABCO to *N*-acetyl-2,4-dimethylaniline (**2d**) (X= CH, R= 2,4-$[CH_3]_2$) and 1.5 equivalents of **1** and hydrolysis the phenylhydrazine (**5**) (R= 2,4-$[CH_3]_2$, R^1= $COCH_3$) was isolated in 64 % yield. The yield of the N-N-forming reaction is obviously higher: With 4-nitrobenzaldehyde the hydrazone (**4**) (R= 2,4-$[CH_3]_2$, R^1= $COCH_3$, R^2= 4-NO_2-C_6H_4) precipitated in 88 %



a - **e**: X= CH (benzenes); **f** - **g**: X= N (pyridines); **h**: X= N(O) (pyridine1-oxides); R,R^1 and R^2see Table 1.

Table 1: Hydrazones (**3**), (**4**) and hydrazines (**5**) from aromatic and heteroaromatic acetamides (**2**), 1-oxa-2-azaspiro[2.5]octane (**1**) and DABCO

com-pound	R	R^1	R^2	mp [°C]	color	base [%][a]	yield [%]
X= CH (benzenes)							
3a	2-CN	H	-	76-77	orange	71	59
4b	2,4-Cl_2	COMe	4-NO_2-C_6H_4	199	yellow	18	58[b]
	2,4-Cl_2	COMe	H	201	red-orange	18	21[c]
3c	2-Br	COMe	-	oil	orange	9	ca. 80
4c	2-Br	COMe	4-NO_2-C_6H_4	219.5	yellow	9	66
	2-Br	COMe	C_6H_5	126	tan-yellow	9	69
						100[d]	71
3d	2,4-Me_2	COMe	-	oil	orange	18	ca. 90
4d	2,4-Me_2	COMe	4-NO_2-C_6H_4	161	pale yellow	18	88
4e	2-MeO	COMe	4-NO_2-C_6H_4	192-194	orange	36	81
5e	2-MeO	COMe	-	49-50	white	-	64
X= N (pyridines)							
3f	2-Cl	H	-	8.5	pale yellow	140	62
4f	2-Cl	H	4-NO_2-C_6H_4	242-243	orange red	140	83
5f	2-Cl	H	-	135-137	pale yellow	140	78
4g	2-$SCH_2C_6H_5$	COMe	4-NO_2-C_6H_4	163	yellow	54	59[e]
						106[f]	49
X= N(O) (pyridine1-oxides)							
3h	2-Cl	H	-	oil	yellow	76	78[b]
4h	2-Cl	H	4-NO_2-C_6H_4	246-248	orange	76	66

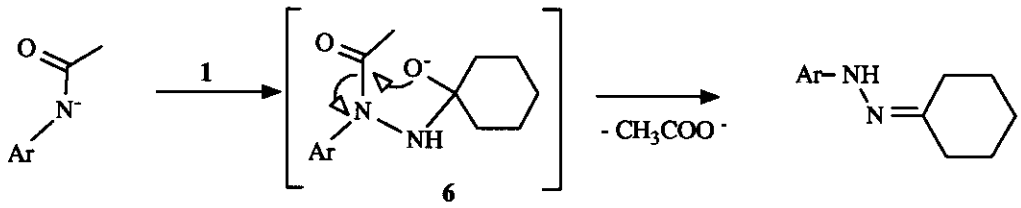
[a] mol% DABCO, referring to starting material (**2**); [b] crude product, + 23 % **2b**; [c] from the second fraction of the recrystallisation of the acetyl compound; [d] urotropine instead of DABCO; [e] + 9% deacylated product (**5g**) (R^1= H); [f] DBU instead of DABCO.

yield. Further examples are shown in Table 1. Analytical data of the compounds (**3** - **5**) are collected in Tables 2 - 3.

The reaction also works with methylsulfonyl or *p*-toluenesulfonylanilines and with other tertiary amines like DBU, *N*-ethylpiperazine, quinuclidine or urotropine, but in general, the yields of phenylhydrazine derivatives are lower. Thus **4c** (R= 2-Br, R^1= $COCH_3$, R^2= C_6H_5) could be isolated using 1 equivalent of urotropine instead of 0.09 equivalents of DABCO.

The primary products (**3**) are easily hydrolyzed by acids to the free hydrazines (**5**), whereas in the 4-nitrobenzylidenehydrazones (**4**) only the acyl group R^1 can be removed by boiling in hydrochloric acid.

On aminating 2-cyanoacetanilide (**3**) (R= 2-CN) the acetyl group is removed. Because of the mild reaction conditions we assume a neighbouring effect acting in the possible intermediate (**6**).



We had observed a similar neighbouring effect in the amination of C-H-acidic compounds, where a nitrile group in α-position to the reaction center was hydrated to a carboxamide group at 0 °C within 5 min.[7]

The tendency of deacylation during amination seems to be predominant in 3-acylaminopyridines with acceptor substituents.

However, in the pyridine series (and analogously in the isoquinoline series) the literature exclusively describes electrophilic aminations forming 1-aminopyridinium compounds, e.g. reactions with *O*-mesitylsulfonylhydroxylamine[8, 9] and hydroxylamine-*O*-sulfonic acid.[10] Even 3-acetylaminopyridine was converted to the corresponding 1-aminopyridinium derivative.[8] In the amination of 3-aminoisoquinolines with *O*-toluenesulfonylhydroxylamine the formation of 3-hydrazinoisoquinolines was excluded.[11]

As to be seen from nmr data (see Table 2) our aminated 3-aminopyridines (**3f**, **4f**, **5f**, and **4g**) show chemical shifts of pyridines and not of 1-aminopyridinium systems. The pyridine1-oxide (**2h**) gives the same amination reaction.

EXPERIMENTAL

The other examples **a** - **e** and **h** are prepared in a similar manner. For the quantities of base used see Table 1. Physical and analytical data are collected in Tables 1 - 3.

2-Chloro-3-cyclohexylidenehydrazinopyridine (3f) (X= N, R= 2-Cl, R^1= H), $C_{11}H_{14}N_3Cl$

0.85 g (5 mmol) of **2f** (X= N, R= 2-Cl, R^1= $COCH_3$) and 7.5 mmol of **1** in toluene (0.2 - 0.4 mol/l)[2] are treated under stirring with 100 mg of DABCO (1,4-diazabicyclo[2.2.2]octane). The temperature raises from 22 to about 26°C. To complete the conversion of the starting material other portions of **1** and the base are added until the exothermic reaction has ceased and the tlc indicates only traces of the starting material. Total amounts of 18 mmol of **1** and 800 mg (7.1 mmol) of DABCO are necessary (in other examples much less, see Table 1!). After filtration and evaporating of volatile material in vacuo (60 °C/0.02 mm Hg) great, pale yellow crystals of the title compound separate from the remaining orange oil.

2-Chloro-3-(4-nitrobenzylidenehydrazino)pyridine (4f) (X= N, R= 2-Cl, R^1= H, R^2= C_6H_4-NO_2-4), $C_{12}H_9N_4ClO_2$

0.1 g (0.45 mmol) of crude oily **3f** are dissolved in 2 ml of 2N HCl, filtered (an extraction of the above amination reaction mixture with 2N HCl is also possible) and treated with 70 mg (0.5 mmol) of 4-nitrobenzaldehyde in 4 ml of ethanol. After 20 min at 60 °C and cooling, the preciptate is washed with ethanol/water (1:1) and recrystallized from ethanol/DMF (12:1).

For the preparation of the benzaldehyde hydrazones the reaction mixture is neutralized with solid sodium hydrogencarbonate.

2-Chloro-3-hydrazinopyridine (5f) (X= N, R= 2-Cl, R^1= H), $C_5H_6N_3Cl$

The oily residue of the amination (or the HCl-extract) is hydrolyzed in 5 ml of 2N HCl 1 h at 40 °C, filtered and extracted twice with ether. The HCl-phase is alkalized by 2N NaOH and extracted with chloroform. Evaporation of the solvent in vacuo yields the hydrazine, pale yellow needles from water, not air-stable.

Table 2: ^{13}C- and ^{1}H-Nmr spectra of the compounds (3) and (4) (lines 1 and 2 of each entry: ^{13}C nmr; lines 3 and 4: ^{1}H nmr chemical shifts in ppm; DMSO-d_6/TMS; 75/300 MHz)

compound	C1[a]	C2	C3	C4	C5	C6	N=C	$COCH_3$	1./3. line: C1/C2,6/C3,5/C4 of $[CH_2]_5$ or R^2
	3. line: ^{1}H								2. line:
									4. line: $[CH_2]_5$ or R^2
3a	148.8	94.8	133.8	118.6	133.9	114.5	154.6	-[b]	
									34.5/26.8/25.4/25.2/26.3
	-	-	7.42	7.29	7.50	6.79	-	-	
									2.41/2.29 (t, 2H), 1.61 (br.s, 6H)
4b[c]	135.4	132.4	133.1	133.6	130.4	128.3	139.2	171.8/21.5	
									140.4/124.1/128.3/148.0
	-	-	7.95	-	7.67	7.51	7.42	2.56	
									8.01 AB 8.26
4c[d]	135.0	122.8	133.8	131.8	131.8	129.8	138.5	171.6/21.6	
									140.4/124.1/128.3/148.0
	-	-	7.90	7.57	7.57	7.43	7.27	2.56	
									7.99 AB 8.25
4c[e]	135.3	123.1	133.8	132.0	131.6	129.7	140.5	171.4/21.6	
									134.1/128.9/127.2/130.1
	-	-	7.89	7.56	7.56	7.41	7.10	2.52	
									7.7 (2H) u. 7.4 (3H)
4d[d]	136.0	129.1	129.1	139.3	132.0	128.4	138.0	171.9/21.7	
									140.7/124.0/128.1/147.8
	-	-	7.28	-	7.20AB7.03[f]		7.42	2.56	
									7.94 AB 8.23
4e[d]	140.7	155.0	113.1	131.4	130.7	121.5	137.7	171.9/21.7	
									140.7/124.1/128.1/147.8
	-	-	7.20	7.13	7.53	7.27	7.26	2.53	
									7.94 AB 8.23
3f	-	134.6	139.4	123.8	120.9	138.2	156.7	-	
									34.8/26.5/25.0/25.2/26.3
	-	-	-	7.70	7.28	7.78			
									2.41/2.30 (t, 2H), 1.6 (br.s, 6H)[g]
4f	-	134.4	138.1	124.2	122.0	140.0*	139.7*	-	
									141.8/124.2/127.1/147.1
	-	-	-	7.91	7.38	7.96	8.44	-	
									7.94 AB 8.25[h]
5f	-	144.4	134.0	119.3	123.8	136.0	-	-	
					-				
	-	-	-	7.48	7.22	7.60			
									NH 6.80 (s, 1H), NH_2 4.22 (s, 2H)
4g	-	157.3	129.2	127.2	121.3	150.4	139.2	171.8/21.6	
									140.3/124.1/128.3/148.0 $CH_2$32.6[i]
	-	-	-	7.73	7.41	8.66	7.28	2.52 Ph 7.1-7.3m	
									7.94 AB 8.25 CH_2 4.46 (AB, J= 14 Hz)
4h	-	140.7	141.3	110.2	123.9	131.5	140.7	-	
									141.4/124.2/127.3/147.8
	-	-	-	7.58	7.33	8.03	8.47		
									7.98 AB 8.28

[a] all starting compounds are considered as 1-acetaminobenzenes, assignments C1 - C6 partly tendentious, [b] NH 9.10s, [c] R^1= $COCH_3$, [d] R^2= 4-NO_2-C_6H_4, [e] R^2= C_6H_5, [f] $J_{H5,H6}$= 8.5 Hz, $J_{H3,H5}$= 2.3 Hz; [g] NH 8.15s; [h] NH 10.57s; [i] Ph C1 137.8, C2/C6 128.9*, C3/C5 128.5*, C4 138.8.

Table 3: Elemental analyses and mass spectra of the compounds (3 - 5)

com-pound	C calcd/found	H	N	Hal or S	Ms (70 eV) [m/z (% rel. intensity)]
3a	73.21 72.88	7.09 7.14	19.70 19.62	- -	213(57), 118(110), 185(95), 90 (51), 96(33), 55(31)
4b[a,b]	51.16 51.67	3.15 3.18	11.93 12.08	20.14 20.46	351/353(5/3), 309/311(100/70), 160/162(23/18), 43(43)
[b,d]					309/311(54/35), 160/162(100/65), 133/135(60/38), 76(36), 50(28)
4c[a,b]	49.74 49.78	3.34 3.34	11.60 11.69	22.06 22.06	361/363(6/6), 319/321(100/98), 320/322(27/14), 170/172(22/20)
4c[a,c]	56.80 56.76	4.13 4.14	8.83 8.78	25.19 25.22	316/318(14/12), 274/276(95/100), 213/215(39/37), 89(43), 172(26)
4d[a,b]	65.58 65.58	5.50 5.53	13.50 13.63	- -	311(20), 269(100), 163(45), 120(98), 119(70), 77(61)
4e[a,b]	61.34 61.37	4.83 4.82	13.41 13.40	- -	313(20), 271(100), 94(30), 122(25), 120(20), 92(20), 272(15), 165(15).
3f[d]	59.06 58.88	6.31 6.34	18.78 18.07	15.85 15.12	223/225(100/35), 188(20), 128/130(40/16), 96(25)
4f[d]	52.09 51.66	3.28 3.25	20.25 20.20	- -	276/278(88/30), 127/129(100/35), 103(25), 102(24), 100(56), 92(68), 76(82), 73(34), 65(41), 64(38), 63(43), 51(36), 50(75)
5f[d]					143/145(52/19), 106(32), 78(100)
4g[a]	62.05 62.22	4.46 4.49	13.79 13.90	7.89 7.95	406(4), 273(10), 239(45), 215(34), 213(46), 181(22), 91(100)
3h[d]					239/141(100/40), 223/225(48/21), 202(22), 188(80), 187(83), 186(38), 160(41), 151(31), 149(36), 144(54), 128(88), 127(52), 110(30), 96(62), 81(50), 79(47), 69(40), 67(38), 55(70)
4h[d]	49.24 48.94	3.10 3.10	19.14 18.96		292/294(100/32), 293/295(15/5), 276/278(18/6), 127(10), 116(13), 76(16)

[a] R^1= $COCH_3$, [b] R^2= 4-NO_2-C_6H_4, [c] R^2= C_6H_5, [d] R^1= H.

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