

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

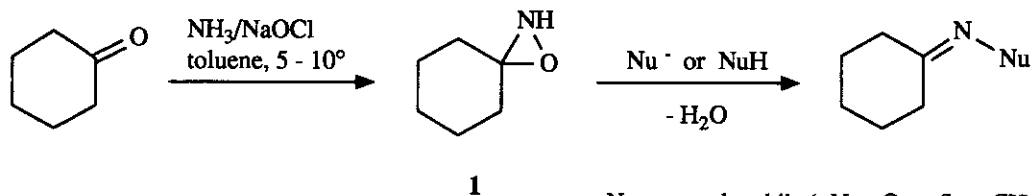
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Dedicated to Prof. Dr. A. R. Katritzky on the occasion of his 65th birthday.

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*-sulfonic² 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

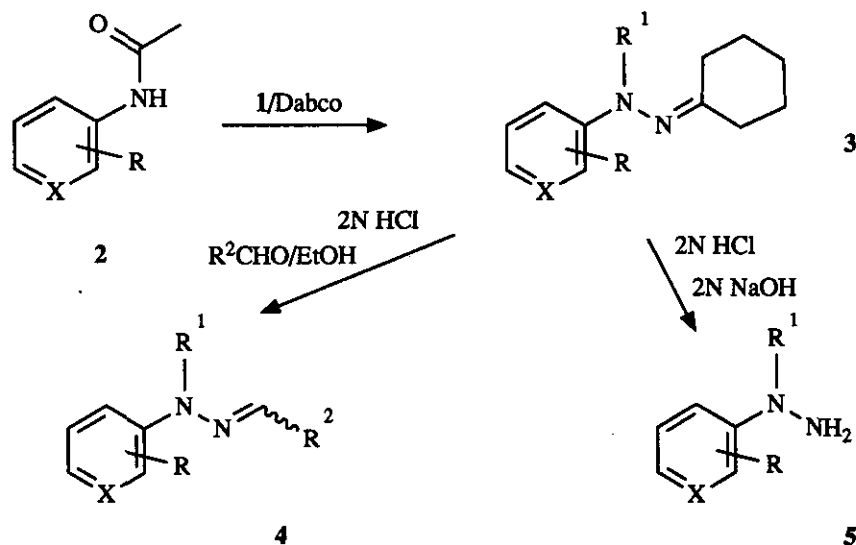


Nu⁻ = nucleophile (>N⁻, -O⁻, -S⁻, >CH⁻)

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-[CH₃]₂) and 1.5 equivalents of 1 and hydrolysis the phenylhydrazine (5) (R = 2,4-[CH₃]₂, R¹ = COCH₃) 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-[CH₃]₂, R¹ = COCH₃, R² = 4-NO₂-C₆H₄) precipitated in 88 %



a - e: X = CH (benzenes); f - g: X = N (pyridines); h: X = N(O) (pyridine 1-oxides); R, R¹ and R² see 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 ₆ H 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 ₆ H ₄	219.5	yellow	9	66
	2-Br	COMe	C ₆ H ₅	126	tan-yellow	9 100 ^{d)}	69 71
3d	2,4-Me ₂	COMe	-	oil	orange	18	ca. 90
4d	2,4-Me ₂	COMe	4-NO ₂ -C ₆ H ₄	161	pale yellow	18	88
4e	2-MeO	COMe	4-NO ₂ -C ₆ H 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 ₆ H ₄	242-243	orange red	140	83
5f	2-Cl	H	-	135-137	pale yellow	140	78
4g	2-SCH ₂ C ₆ H ₅	COMe	4-NO ₂ -C ₆ H ₄	163	yellow	54	59 ^{e)}
						106 ^{f)}	49
X= N(O) (pyridinel-oxides)							
3h	2-Cl	H	-	oil	yellow	76	78 ^{b)}
4h	2-Cl	H	4-NO ₂ -C ₆ H ₄	246-248	orange	76	66

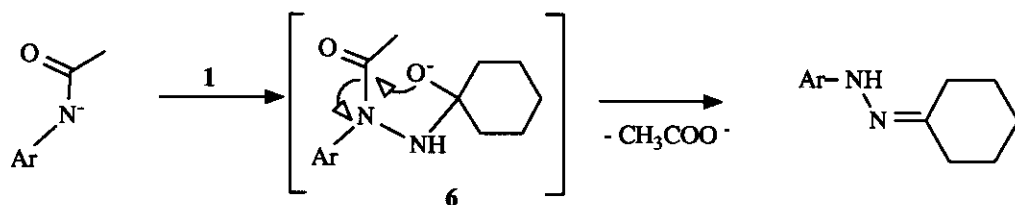
^{a)} mol% DABCO, referring to starting material (2); ^{b)} crude product, + 23 % **2b**; ^{c)} from the second fraction of the recrystallisation of the acetyl compound; ^{d)} urotropine instead of DABCO; ^{e)} + 9% deacylated product (**5g**) (R¹= H); ^{f)} DBU instead of DABCO.

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** ($R = 2\text{-Br}$, $R^1 = \text{COCH}_3$, $R^2 = \text{C}_6\text{H}_5$) 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) ($R = 2\text{-CN}$) 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 pyridine-1-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**) ($X = N$, $R = 2\text{-Cl}$, $R^1 = H$), $C_{11}H_{14}N_3Cl$

0.85 g (5 mmol) of **2f** ($X = N$, $R = 2\text{-Cl}$, $R^1 = COCH_3$) and 7.5 mmol of **1** in toluene ($0.2 - 0.4 \text{ mol/l}$)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**) ($X = N$, $R = 2\text{-Cl}$, $R^1 = H$, $R^2 = C_6H_4\text{-NO}_2\text{-4}$), $C_{12}H_9N_4ClO_2$

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 precipitate 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**) ($X = N$, $R = 2\text{-Cl}$, $R^1 = H$), $C_5H_6N_3Cl$

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

com- pound	C1 ^{a)} 3. line:	C2 3. line:	C3 1H 4. line:	C4 2. line: 4. line:	C5 C1/C2, 6/C3, 5/C4 of [CH ₂] ₅ or R ²	C6 N=C COCH ₃ 1./3. line	N=C COCH ₃ 1./3. line	1./3. line
3a	148.8	94.8	133.8	118.6	133.9 114.5	154.6	- ^{b)}	
	-	-	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	
	-	-	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	
	-	-	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	
	-	-	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	
	-	-	7.28	-	7.20 AB 7.03 ^{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	
	-	-	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	-	
	-	-	-	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*	-	
	-	-	-	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	
	-	-	-	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	-	
	-	-	-	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)} R¹ = COCH₃, ^{d)} R² = 4-NO₂-C₆H₄, ^{e)} R² = C₆H₅, ^{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 calcd/found	N calcd/found	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) R¹ = COCH₃, ^b) R² = 4-NO₂-C₆H₄, ^c) R² = C₆H₅, ^d) R¹ = H.

REFERENCES

- 1 S. Andreae and E. Schmitz, *Synthesis*, **1991**, 327.
- 2 R. G. Wallace, *Aldrichim. Acta*, 1980, **13**, 3 and *Org. Prep. Proc. Int.*, 1982, **14**, 265.
- 3 Y. Tamura, J. Minamikawa, and M. Ikeda, *Synthesis*, **1977**, 1.
- 4 E. Schmitz, R. Ohme, S. Schramm, H. Striegler, H.-U. Heyne, and J. Rusche, *J. Prakt. Chem.*, **1977**, *319*, 195.
- 5 M. Knollmüller and R. Fauss, *Monatsh. Chem.*, 1985, **116**, 1027.
- 6 E. Schmitz and R. Ohme, *Chem. Ber.*, 1964, **97**, 2521.
- 7 S. Andreae, E. Schmitz, J.-P. Wulf, and B. Schulz, *Liebigs Ann. Chem.*, **1992**, 239.
- 8 Y. Tamura, H. J. Kim, Y. Sumida, and M. Ikeda, *J. Pharm. Soc. Jpn.*, 1975, **95**, 1497.
- 9 Y. Tamura, Y. Sumida, Y. Miki, and M. Ikeda, *J. Chem. Soc., Perkin Trans. 1*, **1975**, 406.
- 10 R. Gösl and A. M. Meuwesen, *Org. Synth.*, 1963, **43**, 1.
- 11 A. Messmer and Gy. Hajos, *J. Org. Chem.*, 1981, **46**, 843.

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