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Synthesis of 4-Dialkylaminoquinazolines from the Reaction of N-Aryl Nitrilium Salts with Dialkylcyanamides

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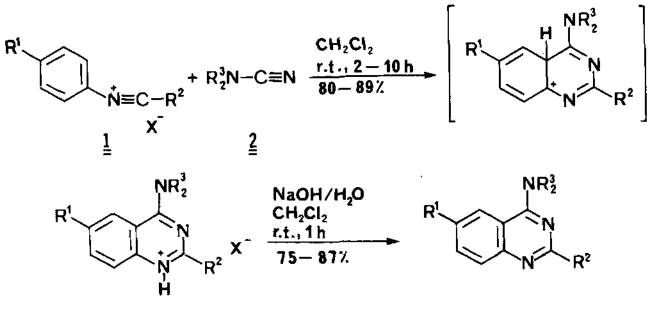
The formation of quinazolines by condensation of nitriles with imidoyl chlorides (or nitrilium salts) in the presence of a Lewis acid had been poineered by Meerwein and co- workers [1]. With the development of new methods for the synthesis of nitrilium salts [2–6], the Meerwein synthesis should find broader applications. Here, I wish to report on the reaction of nitrilium salts **1** with dialkylcyanamides **2** to give salts **3**, from which 4-dialkylaminoquinazolines **4** are obtained with base (Scheme 1).

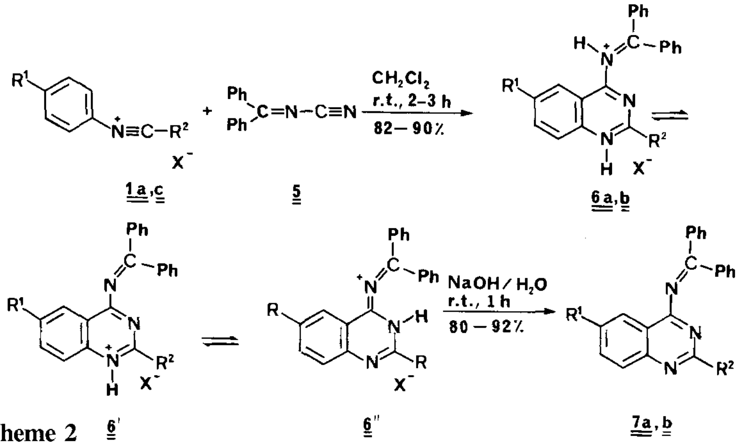


Scheme 1

1–4 x = $SbCl_6$	R^1	R^2	R^3
a	H	Ph	Me
b	H	Ph	*i*-Pr
c	Cl	$4\text{-}ClC_6H_4$	Me
d	Cl	$4\text{-}ClC_6H_4$	*i*-Pr
e	H	Me	Me
f	H	$PhCH_2$	Me
g	Cl	Me	Me

The structural assignments of the new compounds are based on elemental and spectroscopical analyses (Table 1 and Table 2).

Noteworthy is the reaction of the nitrilium salts (**1a,c**) with diphenylalkylidene cyanamide (**5**). The reaction proceeds smoothly furnishing the salts **6a,b** (Scheme 2). Several tautomeric forms can be formulated for **6**, among them is the allenium form **6''**. However, according to the spectral data, compounds **6** are iminium salts with a protonated exocyclic nitrogen atom.



Scheme 2

6,7	R^1	R^2
a	H	Ph
b	Cl	$4\text{-}ClC_6H_4$

Table 1 Selected NMR-and IR-Data, Yields, Melting Points, and Times for the Preparation of the New Compounds

Product	^{1}H-NMR(CD_3CN/ TMS), δ (Hz)$^{b)}$	^{13}C-NMR CD_3CN/ TMS)$^{b)}$, δ	IR(KBr) (cm^{-1})	Yield %	m.p. [°C]	R$^{c)}$ [h]
3a	3.69(CH_3), 11.39(NH)$^{d)}$	43.8(br,CH_3), 112.9, 119.6, 128.1, 129.0, 129.7, 130.3, 131.6, 134.8, 136.6 (Aryl), 155.8, 162.7 (C=N)$^{d)}$	3361 1613 1563	86	244–246 dec	10
3b	1.64(br,CH3) 4.55(br,CH) 11.44(br,NH)$^{e)}$	21.5(CH3, 54.2 br,CH),122.8, 119.6, 127.8, 129.3, 130.3, 131.8, 134.4, 136.2, 141.8 (Aryl), 154.4, 163.2 (C=N)$^{e)}$	3330 1601 1567	89	238–241 dec	10
3c	3.65, 3.74(CH3) 11.49(br,NH)$^{f)}$	44.0(br,CH3), 113.9, 121.4, 128.0, 130.0, 136.9, 140.1, 140.9 (Aryl), 155.0, 161.8 (C=N)$^{f)}$	3315 1613 1598	88	229–231 dec	6
3d	1.76(d,J=4.8, CH_3), 4.62–4.88 (v.br, CH), 13.00(brNH)$^{h)i)}$	21.3(CH_3), 53.9 (br,CH), 113.8, 121.8, 126.9, 130.4, 130.9, 132.3, 136.4, 140.2, 140.4 (Aryl), 153.7, 162.1 (C=N)$^{h)i)}$	3261 1601 1551	86	233–235 dec	6
3e	2.62(CH_3), 3.58, 3.66(CH_3), 11.22(br,NH)$^{j)}$	22.5(CH_3), 42.6, 44.1(CH_3), 112.2, 118.6, 127.5, 128.9, 136.3, 140.8 (Aryl), 159.2, 162.5 C=N)$^{e)}$	3347 1605 1571	80	231–233 dec	10
3f	3.48, 3.65(CH_3), 4.17(CH_2), 11.48(br,NH)	42.1, 42.3, 44.5, (CH_3,CH_2), 112.3, 118.9, 127.8, 128.5, 129,0, 129.7, 130.5, 135.3, 136.4, 140.9 (Aryl), 160.4, 162.4 (C=N)	3349 1605 1567	88	184–187 dec	10
3g	2.60(CH3), 3.53, 3.68(CH3) 11.42(br,NH)	22.5(CH3), 42.5, 44.4(CH3), 113.3, 120.6, 128.1, 132.3, 136.7, 139.8 (Aryl), 159.6, 161.7 (C=N)	3342 1601 1571	87	215–217 dec	6
4a	3.30(s,CH_3)$^{k)}$	41.6(CH_3), 114.8, 124.0, 125.5, 128.4, 128.5, 129.9, 131.9, 138.8, 152.8 (Aryl), 159.1, 163.6 (C=N)$^{k)}$	1613 1567 1517	87	69–70	
4b	1.57(d,J=6.7, (CH_3), 4.23(sep, J=6.7,CH)$^{k)}$	22.0, 50.4(CH), 115.7, 123.6, 124.8, 128.2, 128.4, 128.8, 129.7, 131.5, 139.3, 153.5 (Aryl) 18.8, 163.1 (C=N)$^{k)}$	1613 1586 1559	85	99–100	
4c	3.31(s,CH_3)$^{k)}$	41.7(CH_3), 115.3, 124.6, 128.3, 129.1, 129.6, 130.2, 132.6, 136.2, 137.0, 151.3 (Aryl), 158.3, 162.5 (C=N)$^{k)}$	1613 1578 1520	83	144–145	
4d	1.55(d,J=6.7, CH_3), 4.19 (sep,J=6.7,CH)$^{k)}$	21.9(CH_3), 50.6(CH), 116.3, 124.0, 128.3, 128.9, 129.7, 130.2, 132.4, 136.0, 137.3, 151.7 (Aryl), 157.9, 162.3 (C=N)$^{k)}$	1608^{g} 1582 1524^{g} 1502	75	139–140	
4e	2.64(s,CH_3), 3.25(s,CH_3)$^{k)}$	26.3(CH_3), 41.6(CH_3), 114.1, 123.4, 125.3, 127.5, 131.6, 152.4 (Aryl), 162.7, 163.7 (C=N)$^{k)}$	1613 1562 1516	83	41–43	
4f	3.13(CH_3) 4.18(CH_2)$^{k)}$	41.5(CH_3), 46.3(CH_2), 114.3, 123.7, 125.3, 126.0, 127.8, 128.0, 129.4, 131.7, 139.2, 152.5 (Aryl), 163.4, 164.2 (C=N)$^{k)}$	1612 1567 1516	86	95–97	
4g	2.62(CH_3 3.33(CH_3)$^{k)}$	26.3(CH_3), 41.8(CH_3), 114.7, 124.6, 128.7, 129.2, 132.7, 150.8 (Aryl), 162.8, 163.3 (C=N)$^{k)}$	1608 1567 1516	83	130–131	
6a	12.67(br,NH)	116.3, 120.5(br), 127.8, 129.4, 129.9, 130.3, 130.6, 130.7, 131.1, 131.2, 131.4, 133.5 (Aryl), 159.2(br), 173.1 (br), 174.1 (C=N)	3280 1663^{g} 1551	82	205–208 dec	2^{c}
6b	12.72, 11.90 (br,NH)	large number of lines	3295 1617 1594	90	219–221 dec	3^{c}
7a		–l)	1632 1570	92	154–156	
7b		116.8, 124.8, 126.4, 128.1, 128.3, 128.4, 129.4, 130.1, 133.5, 136.8, 138.4, 151.5, 160.5 (Aryl), 169.0, 171.2 (C=N)$^{k)}$	1644 1582	80	201–202	

$^{a)}$ Satisfactory microanalyses obtained: C ± 0.30, H ± 0.27, N ± 0.36 $^{b)}$ At 295K $^{c)}$ Stirring time for the preparation of **3** and **6** $^{d)}$ At 323K $^{e)}$ At 303K $^{f)}$ At 333K $^{g)}$ Shoulder $^{h)}$ At 284K $^{i)}$ In Acetone-d_6 $^{j)}$ AT 313K $^{k)}$In $CDCl_3$ $^{l)}$ Low solubility

Table 2 Elemental Analysis Data of Compounds **3**, **4**, **6** and **7**

Compound	Formula	Elemental Analysis[a] Calcd./Found		
No.	(MW)	C	H	N
3a	$C_{16}H_{16}Cl_6N_3Sb$	32.82	2.76	7.19
	(584.8)	33.09	2.66	7.33
3b	$C_{20}H_{24}Cl_6N_3Sb$	37.48	3.77	6.56
	(640.0)	37.51	3.74	6.42
3c	$C_{16}H_{14}Cl_8N_3Sb$	29.40	2.16	6.43
	(653.7)	29.60	2.43	6.36
3d	$C_{20}H_{22}Cl_8N_3Sb$	33.83	3.12	5.92
	(709.8)	33.96	3.14	5.77
3e	$C_{11}H_{14}Cl_6N_3Sb$	25.28	2.70	8.04
	(522.7)	25.24	2.68	7.98
3f	$C_{17}H_{18}Cl_6N_3Sb$	34.10	3.03	7.02
	(598.8)	34.01	2.99	6.91
3g	$C_{11}H_{13}Cl_7N_3Sb$	23.71	2.35	7.54
	(557.2)	23.80	2.38	7.50
4a	$C_{16}H_{15}N_3$	77.08	6.06	16.85
	(249.3)	76.81	6.09	16.92
4b	$C_{20}H_{23}N_3$	78.65	7.59	13.76
	(305.4)	78.45	7.61	13.54
4c	$C_{16}H_{13}Cl_2N_3$	60.39	4.12	13.21
	(318.2)	60.33	4.11	13.23
4d	$C_{20}H_{21}Cl_2N_3$	64.18	5.66	11.23
	(374.3)	64.14	5.74	11.27
4e	$C_{11}H_{13}N_3$	70.56	7.00	22.44
	(187.2)	70.26	6.99	22.70
4f	$C_{17}H_{17}N_3$	77.54	6.51	15.96
	(263.3)	77.24	6.42	16.00
4g	$C_{11}H_{12}ClN_3$	59.60	5.45	18.94
	(221.8)	59.77	5.45	18.84
6a	$C_{27}H_{20}Cl_6N_3Sb$	44.98	2.80	5.83
	(721.0)	45.06	2.99	6.14
6b	$C_{27}H_{18}Cl_8N_3Sb$	41.06	2.30	5.32
	(789.8)	40.83	2.34	5.22
7a	$C_{27}H_{19}N_3$	84.13	4.97	10.90
	(385,5)	83.86	4.96	10.83
7b	$C_{27}H_{17}Cl_2N_3$	71.37	3.77	9.25
	(454.3)	71.09	3.87	8.89

[a] Microanalysis were performed by CHN-Mikroanalyse Laboratories/Fakultät Chemie – Universität Konstanz (FRG).

^{13}C-nmr spectra of compounds **3** and **4** exhibit two characteristic signals between 153 – 164 ppm, which have been assigned for the C=N carbons of the quinazoline ring. **6a** exhibits two signals at 173.1 and 174.1 ppm. According to Schmidt the Meerwein quinazoline synthesis proceeds via a polar $[4^+ + 2]$ cyclization [7].

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Experimental

The melting points are uncorrected. Infrared-spectra were recorded on a Mattson Polaris FTIR spectrometer. ^1H and ^{13}C-NMR spectra (δ-scale) were recorded on Bruker-WM-250 and AC-250 spectrometers, with tetramethylsilane as internal standard. All solvents were dried by standard methods. All experiments were conducted with exclusion of moisture. The nitrilium salts **1a,c,e,g** were prepared according to known procedures [5,6].

N-Phenyl-phenylacetonitrilium hexachloroantimonate (**1f**)

A solution of $SbCl_5$ (5.98g, 20 mmol) in CH_2Cl_2 (20 ml) is added dropwise to a cold solution of deoxy benzoin o-(chloro-oxalyl) oxime (6.64 g, 22 mmol), prepared in CH_2Cl_2 (20 ml) without further characterization according to Ref. [5] in CH_2Cl_2 (20 ml). The mixture is stirred at –40°C for 1h, then at 23°C for 1h. The precipitate is filtered off and washed with CH_2Cl_2 (2·30 ml) affording a pale yellow powder (7.40g, 70%); m.p. 122–123°C(dec.).

4-Alkylaminoquinazolinium hexachloroantimonates (**3**) *and* (**6**)

(General Procedure) A mixture of the nitrilium salt (**1**) (10 mmol) and the appropriate cyanamide (**2** or 5) (11 mmol) in CH_2Cl_2 (30 ml) is stirred at 25 C for several hours (Table 1). Et_2O (50 ml) is added. The orange (**3a, 3b, 3e, 3f, 3g**) or yellow (**3c, 3d, 6a, 6b**) precipitate is filtered off and washed with Et_2O to afford the analytically pure product, which can be recrystallized from hot CH_3CN (10 ml) (**3a, 3e, 3c, 3g**); CH_3CN (10 ml)/Et_2O (30 ml) at –20°C (**3b, 3f, 6a**); CH_2Cl_2 (10 ml) + CH_3CN (2 ml)/Et_2O (30 ml) at –20°C (**3d, 6b**).

4-Dialkylaminoquinazolines (**4**) *and* (**7**)

(General Procedure) To a suspension of the salt **3** or **6** (10 mmol) in CH_2Cl_2 (30 ml), aqueous NaOH (10%, 30 ml) is added. After stirring for 1h the organic layer is separated and washed with H_2O (4 x 50 ml). Drying over Na_2SO_4 and evaporation of the solvent gives **4** as a colorless powder (**4f**: brown powder, **4d, 7a,** and **7b**: pale yellow powder), which is recrystallized from n-pentane (20 ml) at –20°C (**4a, 4b, 4c, 4e, 4g**); CH_2Cl_2 (3 ml)/pentane (30 ml) at –20°C (**4d, 4f, 7a**).

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