Synthetic Applications of Aminochlorocarbenes: A Two-step Conversion of *N*-Methylformanilides into 3-Arylamino-2-chloroindoles

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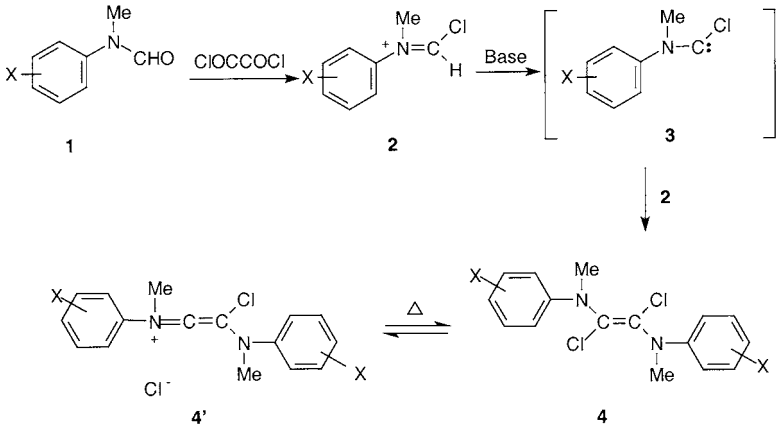
Abstract: The thermal cyclisation of 1,2-diarylamino-1,2-dichloroethenes (dimers of arylaminochlorocarbenes) in DMF affords 3-arylamino-2-chloroindoles in good yields (70–91%).

Key words: cyclisation, 1,2-diarylamino-1,2-dichloroethenes, arylaminochlorocarbenes, 3-arylamino-2-chloroindoles

We have shown in earlier work[1] that Vilsmeier reagents **2** are readily deprotonated with mild bases to yield aminochlorocarbenes (**3**, Scheme 1). Under these conditions, nucleophilic carbenes **2** tend to react with the Vilsmeier reagent to give, after deprotonation a 1,2-diamino-1,2-dichloroethene **4**. We showed that these systems are useful precursors to isatins, 2,2-bis-indoles and to indoloquinolines.[1] We herein demonstrate that the dimers **3** derived from *N*-methylformanilides undergo a facile thermal cyclisation to give 3-arylamino-2-chloroindoles in good yields.

Indoles are among the most important ring systems in the alkaloids and thus are of considerable pharmacological interest. Over one thousand such alkaloids are known.[2] 3-Amino-2-chloroindoles are little known[3] systems and examples of 3-arylamino-derivatives are unknown. The above-mentioned dimers **4** proved of limited stability, requiring storage at low temperature in many cases. At ambient temperature they decomposed on standing. While examining the nature of this decomposition, we observed in one case the conversion of the dimer **4** into an indole at room temperature, as well as in the mass spectrometer (see below). The dimers as highly nucleophilic alkenes, were possibly in equilibrium with their ionic electrophilic analogues, the keteniminium salts **4′**, and the interaction of these two systems would lead to oligomeric material. With a view to studying the reactivity of aminochlorocarbenes **3** and their derived dimers **4**, we therfore thermolysed a variety of 1,2-bis(arylamino)-1,2-dichloroethene **4** in refluxing DMF. Gratifyingly, these dimers did not decompose in hot DMF but instead cyclised to yield novel indoles, namely 2-chloro-3-(*N*-arylamino)indoles **5** in good yields (Scheme 2). Although the photo-cyclisation of *N*-vinylanilines [$\pi_2s+\pi_2s+\sigma_2a$] to indoles is well documented[4] the thermal equivalent is disallowed, supporting the keteniminium-mediated mechanism.

This unexpected result prompted us to optimise the preparation of the dimers **4**. In our earlier work,[1] we obtained *N*-methyl-*N*-(p-halophenylamino)-1,2-dichloroethenes **4a**–**c** by treating the Vilsmeier's reagents **2a**–**c** with Hünig's base at 0–35 °C in chloroform or THF solution. The dimers **4**, bearing electron-donating groups were



Scheme 1

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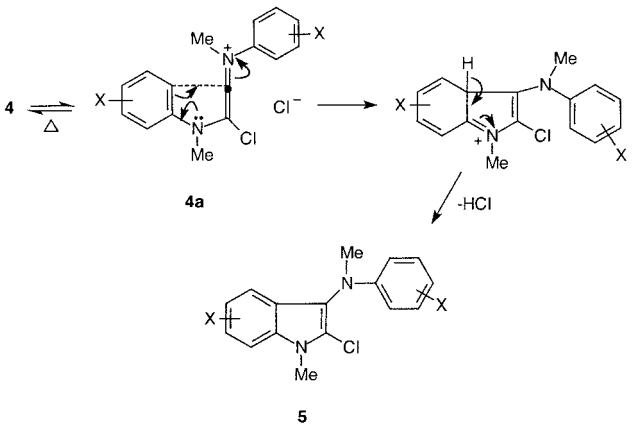


4 and 5	a	b	c	d	e	f	g	h
X	*p*-F	*p*-Cl	*p*-Br	H	*p*-Me	*p*-OMe	*m*-Cl	*m*-Br

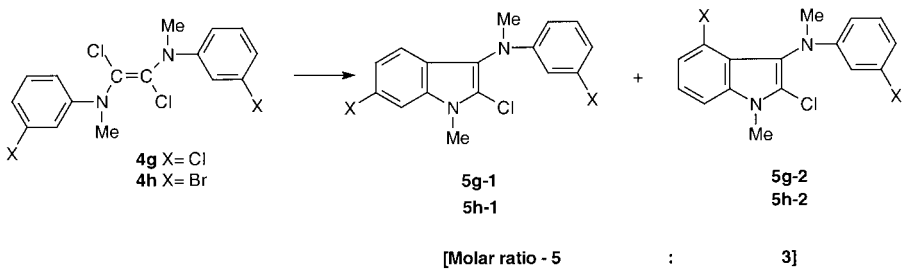
Scheme 2

not isolated, being unstable under the reaction conditions. Indeed, we now find that these dimers are unstable even in chloroform solution. Furthermore, they are sensitive to oxygen, heat, acidic conditions, and silica gel. The most stable dimers are the 4-bromo- and 4-chloro-derivatives, **4b** and **4c**, which can be kept at room temperature for several days. The others, **4a** and **4d**–**h** are only stable below –10 °C. The dimers **4d**–**g** prove to be particularly unstable, becoming dark in a few hours at room temperature. With these observations in mind, we prepared the dimers **4** under more appropriate reaction conditions. The best results are shown in Table 1. The structures of the dimers have been identified by their IR, ^{1}H NMR, ^{13}C NMR, MS, CHN analysis or HRMS. All the dimers are white solids except **4g**, which is a colourless oil and partly cyclises to give the indole **10g** even at room temperature in about half an hour. Consequently, this oily dimer did not give satisfactory elemental analysis data, and the HRMS of **4g** also revealed the molecular weight of **5g**, not **4g**, suggesting that this dimer cyclised under HRMS conditions.

We initially obtained the indole derivative **5b** from dimer **4b** in refluxing DMF. When we used the same conditions to prepare the other indoles, we found many of the dimers were not stable and the reaction mixture became very dark. However, lower temperatures and added piperidine (as a hydrochloric acid trap) proved effective (Table 2). While the symmetrical, *para*-substituted phenylaminoethenes **4a**–**f** afforded only one type of indoles **5a**–**f**, the cyclization of *meta*-substituted dimers **4g** and **4h,** gave both possible regioisomeric indoles. The major products are those from cyclisation at the less hindered position, the ratio of two products being about 5:3 (Scheme 3).

Table 1 Optimised Reaction Conditions for Dimer **4** Formation and their Yields

1–**4** X	Solvent	Temp. (°C)	Time (h)	Product	Yield (%)
p-F	$CHCl_3$	–10 to 25	3	**4a**	72
p-Cl	$CHCl_3$	–10 to25	4	**4b**	52
p-Br	$CHCl_3$	–10 to 25	4	**4c**	68
H	THF	–10 to 25	3	**4d**	85
p-Me	xylene	–78 to 25	6	**4e**	76
p-OMe	THF	–78 to 25	6	**4f**	50
m-Cl	$CHCl_3$	–10 to 25	4	**4g**	55
m-Br	$CHCl_3$	–10 to 25	3	**4h**	85



Scheme 3

Table 2 Optimised Reaction Conditions for the Formation of the Indoles **5** and their Yields

Starting material	Base	Solvent	Temp. (°C)	Time (h)	Product	Yield (%)
4a	piperidine	DMF	110–120	7	**5a**	91
4b	–	DMF	140–160	7	**5b**	79
4c	–	DMF	140–160	5	**5c**	70
4d	piperidine	DMF	100–110	8	**5d**	73
4e	piperidine	DMF	100–110	8	**5e**	81
4f	piperidine	DMF	100–110	8	**5f**	78
4g	piperidine	DMF	140–150	10	**5g-1** **5g-2**	51 30
4h	piperidine	DMF	140–150	18	**5h-1** **5h-2**	51 32

Table 3 Spectroscopic Data for the Dimers **4**

Dimers **4**	Mp (°C)	IR (cm^{-1})	^1H NMR (C_6D_6) δ, *J* (Hz)	^{13}C NMR (C_6D_6) δ	MS (EI) *m*/*z* (%)
4a	132[a]	1506, 1468	6.96 (2 H, t, *J* = 8.7 Hz), 6.71 (2 H, m), 2.79 (3 H, s)	159.2, 157.3, 141.5, 134.3, 116.7/116.8 (d), 116.2/116.0 (d), 37.2	272 (82), 291 (59), 306 (100), 432 (15) [M^+]
4b	168[a]	1592, 1490	7.29 (2 H, d, *J* = 8.9 Hz), 6.80 (2 H, d, *J* = 8.9 Hz), 3.17 (3 H, s)	143.3, 133.6, 129.2, 125.9, 116.0, 37.1	111 (100), 222 (65)/224 (60), 338 (60)/340 (55), 374 (30) [M^+]/376 (35)/378 (20)/380 (10)
4c	144–146[a]	1589, 1488, 1465	7.33 (2 H, d, *J* = 9.0 Hz), 6.41 (2 H, d, *J* = 8.9 Hz), 2.94 (3 H, s)	148.1, 133.6, 132.1, 125.4, 114.8, 39.5	312 (47)/314 (46), 426 (43) [M^+ – HCl]/ 428 (100)/ 430 (70)
4d	129–132[a]	1595, 1579, 1495,1471	7.18 (2 H, t, *J* = 7.7 Hz), 6.91 (1 H, t, *J* = 7.8 Hz), 6.77 (2 H, d, *J* = 8.5 Hz), 2.63 (3 H, s)	146.2, 137.1, 129.5, 120.8, 115.5, 37.5	117 (93), 219 (100)/220 (93), 234 (88)/235 (60)/236 (32), 270 (94)/272 (30), 306 (6.2) [M^+]/ 308 (3.6)
4e	130[a]	1611, 1512	7.15 (2 H, d, *J* = 8.4 Hz), 6.97 (2 H, d, *J* = 8.4 Hz), 2.95 (3 H, s), 2.26 (3 H, s)	143.3, 134.7, 130.8, 130.2, 115.7, 37.1, 20.7	91 (90), 298 (100), 334 (70) [M^+]/336 (40)/338 (10)
4f	132[a]	1509, 1470, 1442	6.98 (2 H, d, *J* = 9.2 Hz), 6.94 (2 H, d, *J* = 9.2 Hz), 3.49 (3 H, s), 2.97 (3 H, s)	155.2, 139.5, 134.7, 117.3, 115.2, 55.3, 37.5	77 (100), 92 (85), 315 (60), 330 (85)/332 (30), 366 (10) [M^+]/368 (8)
4g	Oil[b]	1594, 1571, 1482	7.21 (1 H, t, *J* = 8.1 Hz), 6.91(1 H, d, *J* = 7.9 Hz), 6.81 (1 H, s), 6.72 (1 H, dd, *J* = 8.2, 1.7 Hz), 2.96 (3 H, s)	147.1, 136.3, 135.5, 130.5, 120.8, 115.4, 113.4, 38.0	111 (75), 268 (100)/270 (30), 338 (50)/336 (45), 376 (8) [M^+]/ 378(4)
4h	81–83[a]	1589, 1480, 1561	7.14 (1 H, t, *J* = 8.0 Hz), 7.05 (1 H, d, *J* = 8.3 Hz), 6.95 (1 H, s), 6.75 (1 H, dd, *J* = 8.2, 1.4 Hz), 2.95 (3 H, s)	147.3, 136.5, 131.2, 123.5, 123.0, 118.0, 114.4, 37.8	461.8900 [M^+]

[a] Elemental analysis: C ± 0.4, H ± 0.5, N ± 0.2.
[b] HRMS: *m*/*z* calcd for $C_{16}H_{14}Br_2Cl_2N_2$, 461.8894; found: 461.8900.

In summary, we herein have discovered a very simple and efficient method for preparing 3-arylamino-2-chloroindoles in a two-step route from *N*-methylformanilides. These steps involve formation of the corresponding Vilsmeier reagents, conversion into aminochlorocarbenes with Hünig's base and thermal cyclisation of the derived dimers of these carbenes.

Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR were obtained on a Bruker Avance 500. IR spectra were recorded using an AVATAR 360 FT-IR spectrometer. Mass spectra were recorded on a Trace MS instrument (EI-MS) or Bruker APEX-2 (HRMS) and elemental analyses were performed on a GMBH Vario EL instrument. Light petroleum refers to the fraction bp 60–80 °C.

Dimers 4; General Procedure

Under a nitrogen atmosphere, oxalyl chloride (1.40 g, 0.96 mL, 0.011 mol) was added dropwise to an *N*-methylformanilide **1** (0.01 mol) cooled in an ice-bath to form a solid Vilsmeier's reagent. A soln of Hünig's base (1.42 g, 1.92 mL, 0.011 mol) in an appropriate solvent (50 mL) was added slowly to the Vilsmeier's reagent below

Table 4 Spectroscopic Data of the Indoles **5**

Indole	Mp (°C)	IR (cm^{-1})	^{1}H NMR δ, *J* (Hz)	^{13}C NMR δ	MS (EI) *m*/*z* (%)
5a	67–68[a]	1550, 1508, 1487	7.26–7.28 (1 H, m), 6.99–7.03 (1 H, m), 6.90–6.96 (3 H, m), 6.59–6.62 (2 H, m), 3.80 (3 H, s), 3.32 (3 H, s)[c]	159.4, 157.5, 157.2, 145.6, 131.5, 124.9, 115.7/115.8 (d), 113.9/114.0 (d), 111.2, 110.9, 110.6/110.7 (d), 103.6/103.8 (d), 39.7, 30.6	95 (57), 241 (50), 255 (55)/256 (85), 291(65), 306 (100) [M$^+$]/308 (35)
5b	101–102[a]	1599, 1549, 1493, 1469	7.63 (1 H, d, *J* = 8.7 Hz), 7.26 (1 H, dd, *J* = 8.7, 1.7 Hz), 7.21 (1 H, s), 7.17 (2 H, d, *J* = 8.9 Hz), 6.57 (2 H, d, *J* = 8.9 Hz), 3.80 (3 H, s), 3.26 (3 H, s)[d]	148.2, 133.7, 129.5, 125.9, 125.1, 124.4, 123.1, 121.7, 118.9, 117.2, 114.9, 113.2, 39.8, 31.2	268 (100)/270 (35), 338 (97) [M$^+$]/340 (85)/342 (35)
5c	136–137[a]	1589, 1489, 1466	7.43 (1 H, d, *J* = 1.6 Hz), 7.35 (1 H, dd, *J* = 8.7, 1.8 Hz), 7.27 (2 H, d, *J* = 9.5 Hz), 7.22 (1 H, d, *J* = 8.7 Hz), 6.57 (2 H, d, *J* = 9.0 Hz), 3.79 (3 H, s), 3.32 (3 H, s)[c]	148.1, 133.6, 132.1, 125.7, 125.4, 124.8, 120.8, 119.1, 114.8, 114.2, 111.4, 109.8, 39.5, 30.6	314 (40)/316 (41), 426 (45) [M$^+$] /428 (100)/430 (70)
5d	68–69[a]	1599, 1576, 1499, 1465	7.46 (1 H, d, *J* = 7.9 Hz), 7.24–7.31 (3 H, m), 7.12 (1 H, t, *J* = 7.5 Hz), 7.01 (1 H, d, *J* = 8.2 Hz), 6.87–6.92 (3 H, m)[e]	149.3, 135.0, 129.3, 124.0, 123.4, 122.6, 120.4, 120.1, 118.7, 117.5, 113.2, 109.7, 39.4, 30.3	220 (95), 235 (50), 255 (40), 270 (100) [M$^+$]/272 (30)
5e	80–81[a]	1617, 1515	7.29 (1 H, d, *J* = 8.5 Hz), 7.04 (1 H, d, *J* = 8.3 Hz), 7.05 (1 H, s), 6.92 (2 H, d, *J* = 8.3 Hz), 6.55 (2 H, d, *J* = 8.5 Hz), 3.71 (3 H, s), 3.28 (3 H, s), 2.32 (3 H, s), 2.19 (3 H, s)[f]	147.5, 133.7, 130.0, 129.7, 129.5, 126.0, 124.2, 122.8, 119.8, 117.9, 113.1, 110.0, 39.0, 29.8, 21.1, 20.0	247 (65), 262 (100), 298 (38) [M$^+$]/300 (14)
5f	80–81[a]	1619, 1510, 1488	7.39 (1 H, d, *J* = 9.0 Hz), 6.86 (1 H, dd, *J* = 8.9, 2.1 Hz), 6.76 (2 H, d, *J* = 9.0 Hz), 6.70 (1 H, s), 6.59 (2 H, d, *J* = 8.9 Hz), 3.78 (3 H, s), 3.70 (6 H, s), 3.29 (3 H, s)[f]	154.9, 152.3, 143.9, 130.4, 127.3, 124.5, 123.0, 120.3, 115.0, 114.7, 114.1, 112.4, 111.2, 100.0, 55.4, 55.3, 39.1, 29.9	280 (55), 300 (50), 515 (85), 330 (100) [M$^+$]/332 (65)
5g-1	107–108[a]	1596, 1562, 1487, 1469	7.33 (1 H, d, *J* = 1.5 Hz), 7.17 (1 H, d, *J* = 8.4 Hz), 7.04 (2 H, m), 6.70 (1 H, d, *J* = 8.7 Hz), 6.62 (1 H, t, *J* = 2.2 Hz), 6.48 (1 H, d, *J* = 8.4 Hz), 3.75 (3 H, s), 3.30 (3 H, s)[c]	150.3, 135.4, 135.2, 130.3, 129.0, 124.0, 122.3, 121.5, 119.6, 119.4, 117.7, 113.0, 111.5, 110.0, 39.5, 30.6	253 (60), 268 (100)/ 270 (55), 338 (90)/ 340 (87)/342 (30)
5g-2	102–104[a]	1594, 1564, 1486	7.27 (1 H, t, *J* = 8.0 Hz), 7.19 (1 H, t, *J* = 7.8 Hz), 7.07–7.12 (2 H, m), 6.69 (1 H, d, *J* = 7.8 Hz), 6.57 (1 H, s), 6.44 (1 H, d, *J* = 8.4 Hz), 3.82 (3 H, s), 3.29 (3 H, s)[c]	151.3, 136.3, 135.3, 130.3, 126.2, 124.6, 123.4, 121.9, 121.6, 118.4, 117.1, 112.7, 111.1, 108.5, 40.4, 30.8	268 (100)/270 (45), 338 (80)/340 (65)/ 342 (35)
5h-1	119–120[a]	1593, 1567, 1485	7.53 (1 H, s), 7.22 (1 H, dd, *J* = 8.4, 0.85 Hz), 7.16 (1 H, d, *J* = 8.4 Hz), 7.03 (1 H, t, *J* = 8.1 Hz), 6.88 (1 H, d, *J* = 7.8 Hz), 6.82 (1 H, s), 6.55 (1 H, dd, *J* = 8.4, 2.2 Hz), 3.78 (3 H, s), 3.33 (3 H, s)[c]	150.4, 135.6, 130.6, 124.1, 123.7, 122.6, 120.6, 119.8, 119.7, 116.5, 115.9, 113.0, 112.0, 39.5, 30.6	312 (75)/314 (700, 426 (40) [M$^+$] /428 (100)/430 (65)
5h-2	120–121[b]	1592, 1559, 1484	7.31 (2 H, d, *J* = 7.9 Hz), 7.14 (1 H, t, *J* = 7.9 Hz), 7.04 (1 H, t, *J* = 8.1 Hz), 6.85 (1 H, d, *J* = 7.8 Hz), 6.75 (1 H, s), 6.47 (1 H, d, *J* = 7.7 Hz), 3.82 (3 H, s), 3.31 (3 H, s)[c]	151.4, 136.0, 130.5, 126.5, 125.2, 123.8, 123.6, 123.0, 120.0, 118.8, 115.4, 111.9, 111.6, 109.0, 40.4, 30.7	427.9105 [M + 1] (FAB)

[a] Elemenatal analysis: C ± 0.4, H ±0.6, N ± 0.5.
[b] HRMS: *m*/*z* calcd for $C_{16}H_{13}Br_2ClN_2$ (M + 1)$^+$, 427.9108; found, 427.9108.
[c] $CDCl_3$.
[d] DMSO-d_6.
[e] C_6D_6.
[f] CD_3COCD_3.

–10 °C or – 78 °C (see Table 1) and the mixture was stirred for the period of time and at the temperature shown in Table 1. After removal of most of solvent, the residue (about 5–10 mL) was filtered through a pad of neutral alumina, washed with Et_2O (about 300 mL) and evaporated to give the crude product, which was further purified by chromatography through neutral alumina, and eluted using light petroleum–EtOAc, 10:1. The properties of the products are recorded in Table 3.

Indoles 5; General Procedure

Under a nitrogen atmosphere, 1,2-diarylamino-1,2-dichloroethenes **4** (0.005 mol) were dissolved in DMF (15 mL) and piperidine (5 mL). The mixture was heated for a period of time at the temperature shown in Table 2. After removal of DMF and piperidine under vacuum, the product was isolated by chromatography on silica gel, and eluted using light petroleum–EtOAc, 10:1. The properties of the products are recorded in Table 4.

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