Carbenes from Vilsmeier reagents by the action of bases in $POCl_3$; the umpolung of Vilsmeier reagents

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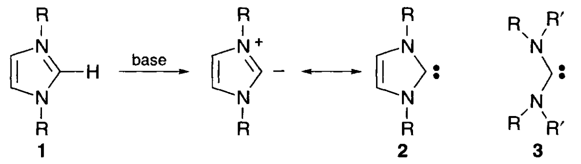
When *para*-substituted *N*-methylformanilides are treated in $POCl_3$ with a base, the corresponding Vilsmeier reagent formed undergoes ready deprotonation to give an amino-chlorocarbene from which a range of products derive; a carba- moyl chloride, *N*-methylisatins, dimers‡ [1,2-dichloro-1,2- bis(*N*-methyl-*N*-arylamino)ethenes], trimers‡ {5,10-dimethyl- 11-(*N*-methyl-*N*-arylamino)-10*H*-indolo[3,2-*b*]quinolinium and 5,10-dimethyl-10*H*-indolo[3,2-*b*]quinolinium salts} and tetramers‡ [1,1′-dimethyl-3,3′-bis(*N*-methyl-*N*-arylamino)-2,2-biindolyl] are isolated, depending upon the base used and the *para*-substituent.

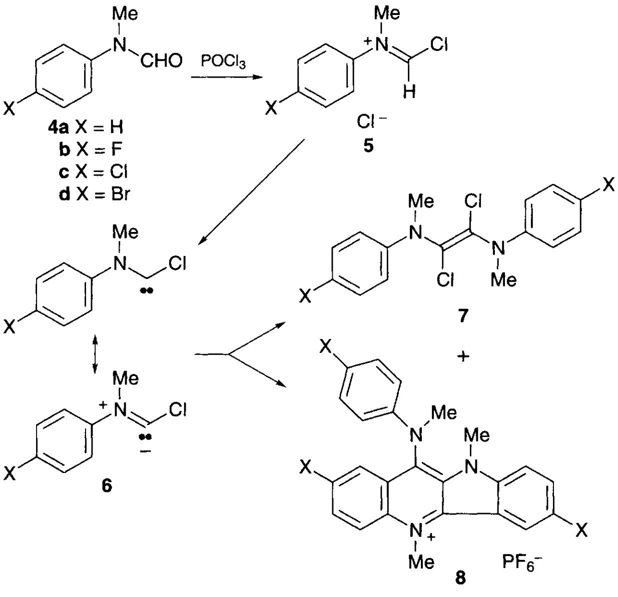
The remarkable developments in the synthesis of stable, isolable diaminocarbenes **2**, stimulated by Arduengo's findings[1] concerning the base-catalysed deprotonation of imidazolium salts **1** (Scheme 1) have been the spur to exploit the chemistry of stable carbenes and to develop this exciting field to other carbene derivatives. Thus stable non-aromatic diaminocarbenes (**3**; *e.g.* R = CH_2CH_2, R = R′ = Pr^i) have also been described, and the need for an 'aromatic' unit shown not to be necessary.[2] Here we describe the ready deprotonation of Vilsmeier reagents under remarkably mild conditions using nitrogen bases in $POCl_3$ solution, giving non-isolated amino-chlorocarbenes from which a variety of products are derived. The stability of this new nucleophilic carbene type should lie between that of diamino- and dichloro-carbenes.

$POCl_3$ is a remarkable solvent in that it allows both electrophilic and nucleophilic reactions to take place.[3] *tert*-Nitrogen bases react as bases in $POCl_3$ solution. *para*-Substituted *N*-methylformanilides **4** rapidly and exothermically form the corresponding chloromethyleniminium salts **5** [Vilsmeier reagents (VR)] on warming in $POCl_3$. On addition of a molar equivalent of a nitrogen base, the solution becomes red and after heating at 80 °C under nitrogen atmosphere (monitored by ^1H NMR) and aqueous work-up, products are formed which are rationalised by invoking the intermediate formation of an aminochlorocarbene **6**. Surprisingly, use of pyridine gives a different range of products to those observed when an aliphatic base is used.

Use of pyridine results in two product types (Scheme 2, Table 1): Thus, quenching the reaction mixture in ice-water and ether and addition of ammonium hexafluorophosphate, causes precipitation of a red solid in most cases, identified by spectroscopic (in particular, electrospray MS, ^1H NMR and difference NOE NMR at the three Me groups) and analytical data as 5,10-dimethyl-11-(*N*-methyl-*N*-phenylamino)-10*H*-indolo[3,2-*b*]quinolinium hexafluorophosphate§ **8** while chromatography of the organic layer from the basified filtrate gives, depending on reaction time, a colourless solid similarly shown to be 1,2-dichloro-1,2-bis(*N*-methyl-*N*-arylamino)-ethene **7**. The formation of the former product **8** from the latter **7** was shown separately. A mechanism of formation of these



Scheme 1

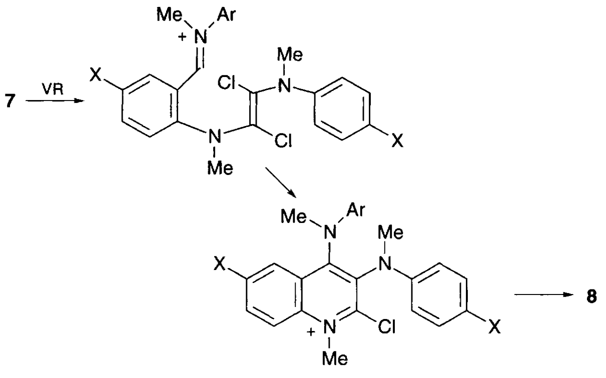


Scheme 2

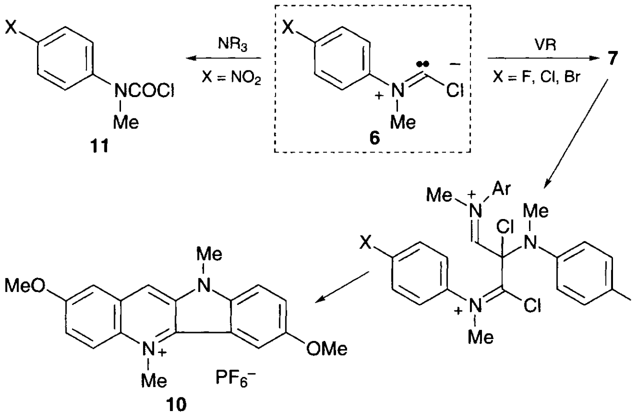
Table 1 Reactions of p-X-C_6H_4NMeCHO with $POCl_3$ and base 80 °C under nitrogen[a]

X	Base[b] r–ct–n time/h	Yield (%) Dimer 7	Trimer 8	10	Tetramer 13	Isatin 12
F	P-5	—	38	—	—	—
F	M-6	—	23	—	28	—
Cl	P-6	22	22	—	—	—
Cl	P-23	—	31	—	—	—
Cl[c]	P-23	—	25	—	—	—
Cl[d]	P-4	13	48	—	—	—
Cl	M-6	—	—	—	26	—
Br	P-23	2	—	—	—	—
Me	M-6	—	12	—	3	—
OMe	M-6	—	—	31	—	—
NO_2	M-6	—	—	—	—	20[e]

[a] The formanilide (0.5 mol) and $POCl_3$ (10 ml) were mixed in an ice bath under N_2, warmed to 80 °C for 5 min. and cooled to *ca.* 0 °C. Pyridine (0.05 mol) was added and the mixture was heated as shown, being monitored by NMR. Quenching in water and addition of ethyl acetate and NH_4PF_6 precipitated **8** as a red solid and the dimer **7** was isolated by flash chromatography of the organic phase. [b] P = pyridine; M = *N*-methylmorpholine. [c] All the reactants were added at the beginning, the reaction being slower. [d] The dimer **7** was reacted with an equimolar amount of p-chloro-*N*-methylformanilide in $POCl_3$. [e] The carbamoyl chloride **11** is also produced (14%).



Scheme 3



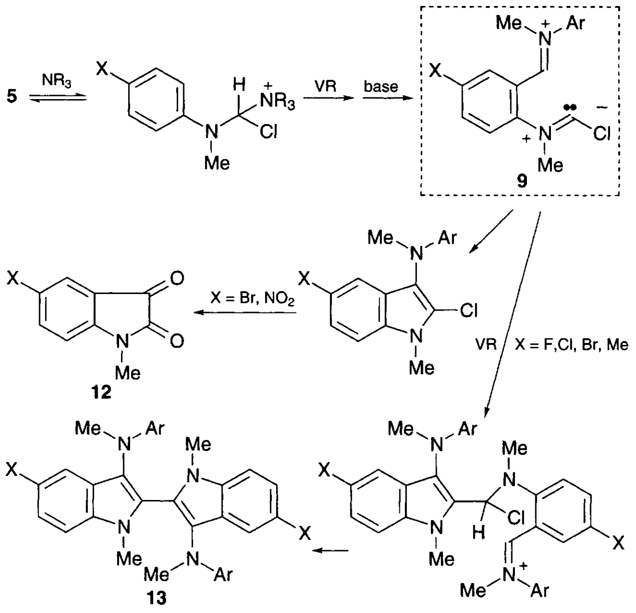
Scheme 4

products is outlined in Scheme 3. Thus formylation of the carbene, now an 'umpoled' Vilsmeier reagent, followed by proton loss leads to the dimer **7**. Further ring formylation of this enamenic dimer and electrocyclisation of the resulting triene (in a manner analogous to the formation of quinolinium salts from Vilsmeier formylation of α-chloroenamines[3]) yields, after further electrophilic cyclisation, the trimer **8**. Curiously, the parent *N*-methylformanilide gave only decomposition products under the reaction conditions.

When a *para*-substituted *N*-methylformanilide **1** in $POCl_3$ is treated with DABCO or better, *N*-methylmorpholine, a variety of products are formed, which we rationalise as being derived either from the carbene **6** or the formylated carbene **9** (Schemes 4 and 5).

Traces of the dimer **7** and quantities of the trimer **8** are again noted. However in one case (**4**, X = OMe) the 11-unsubstituted trimeric red indolo[3,2-*b*]quinoline **10** was the only isolable product, which is expected if alkene-formylation occurs, the ring being deactivated by the *meta* methoxy groups[3] but the alkene being activated. From the *p*-nitroformanilide (**4**, X = NO_2) no red dye was formed but the carbamoyl chloride **11** was isolated, possibly by oxidation of the carbene **6** or by elimination from a dichlorophosphoryliminium salt. These products appear to form from the same carbene **6** or its dimer **7** as with the pyridine mediated reactions.

An alternative pathway prevails to account for the other products (since they are not observed by formylation of the dimer **7**), and we propose that an *ortho*-formylation occurs as shown in Scheme 5. The base reacts with the Vilsmeier reagent to give a covalent intermediate that is activated towards further formylation. (The covalent species is preferred to the conjugated dication that would derive from conversion to a diaminoiminium chloride salt.) This *ortho*-formylated Vilsmeier reagent is now even more acidic at the Vilsmeier proton position and another carbene **9** is formed. Cyclisation of this intermediate followed by aqueous work-up and adventitious aerial oxidation leads to the isatin **12**, which is noted with X = NO_2 (20%) and X = Br (15%). By further formylation and cyclisation of the common intermediate, a pale yellow, fluorescent tetramer is produced in most cases (X = F[28%], Cl[26%], Br[18%], Me [trace], MeO[–], NO_2[–]) for which the structure **13** has been confirmed.§



Scheme 5

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Footnotes

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‡ The terms dimer, trimer and tetramer refer to the number of moles of Vilsmeier reagent incorporated into the product.

§ Structure confirmed by X-ray crystallography which will be reported elsewhere. Thanks to Drs D. Eggleston and C. Haltiwanger of SB for the X-ray crystallography.

References

1 A. J. Arduengo, R. L. Harlow and M. Kline, *J. Am. Chem. Soc.*, 1991, **113**, 361.
2 A. J. Arduengo, J. R. Goerlich and W. J. Marshall, *J. Am. Chem. Soc.*, 1995, **117**, 11 027; R. W. Alder, presented at the RSC Heterocyclic Group Meeting, Kings College, London, 5th January, 1996.
3 See for example O. Meth-Cohn and D. L. Taylor, *Tetrahedron*, 1995, **51**, 12 869.

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