

Carbenes from Vilsmeier reagents by the action of bases in POCl₃; the umpolung of Vilsmeier reagents

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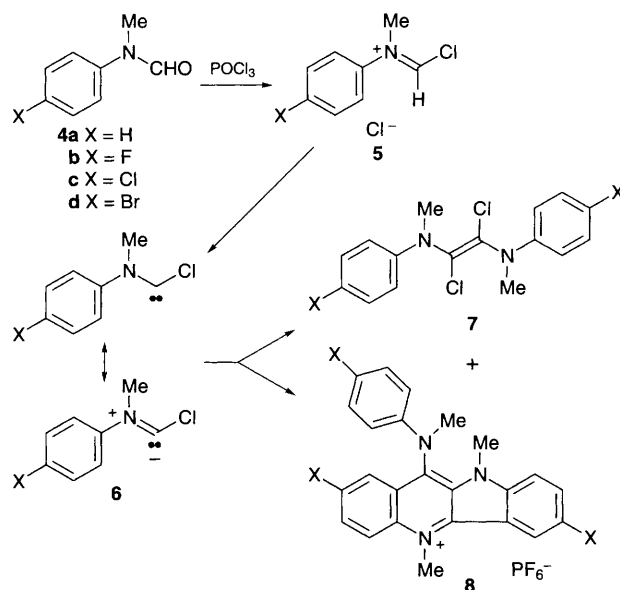
When *para*-substituted *N*-methylformanilides are treated in POCl₃ with a base, the corresponding Vilsmeier reagent formed undergoes ready deprotonation to give an amino-chlorocarbene from which a range of products derive; a carbamoyl chloride, *N*-methylisatins, dimers‡ [1,2-dichloro-1,2-bis(*N*-methyl-*N*-arylamino)ethenes], 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 findings¹ 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 = CH₂CH₂, R = R' = Prⁱ) 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 POCl₃ 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.

POCl₃ is a remarkable solvent in that it allows both electrophilic and nucleophilic reactions to take place.³ *tert*-Nitrogen bases react as bases in POCl₃ solution. *para*-Substituted *N*-methylformanilides **4** rapidly and exothermically form the corresponding chloromethyleniminium salts **5** [Vilsmeier reagents (VR)] on warming in POCl₃. 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 amino-chlorocarbene **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

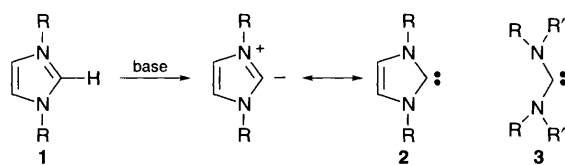


Scheme 2

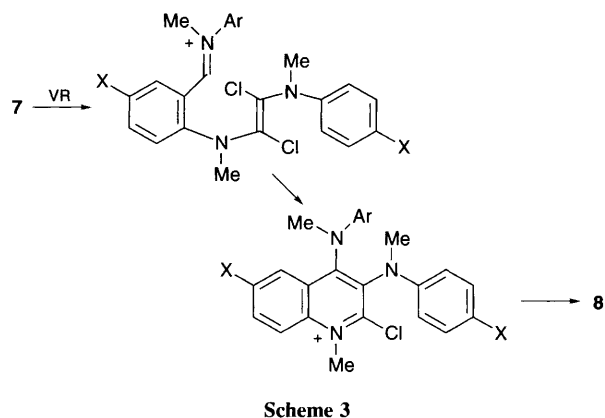
Table 1 Reactions of *p*-X-C₆H₄NMeCHO with POCl₃ and base 80 °C under nitrogen^a

X	Base ^b r-ct-n time/h	Yield (%)				
		Dimer		Trimer		Isatin
		7	8	10	13	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

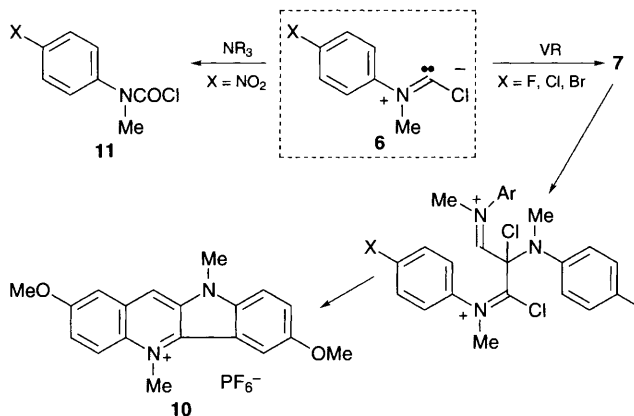
^a The formanilide (0.5 mol) and POCl₃ (10 ml) were mixed in an ice bath under N₂, warmed to 80 °C for 5 min. and cooled to ca. 0 °C. Pyridine (0.05 mol) was added and the mixture was heated as shown, being monitored by NMR. Quenching in water and addition of ethyl acetate and NH₄PF₆ precipitated **8** 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 POCl₃. ^e The carbamoyl chloride **11** is also produced (14%).



Scheme 1



Scheme 3



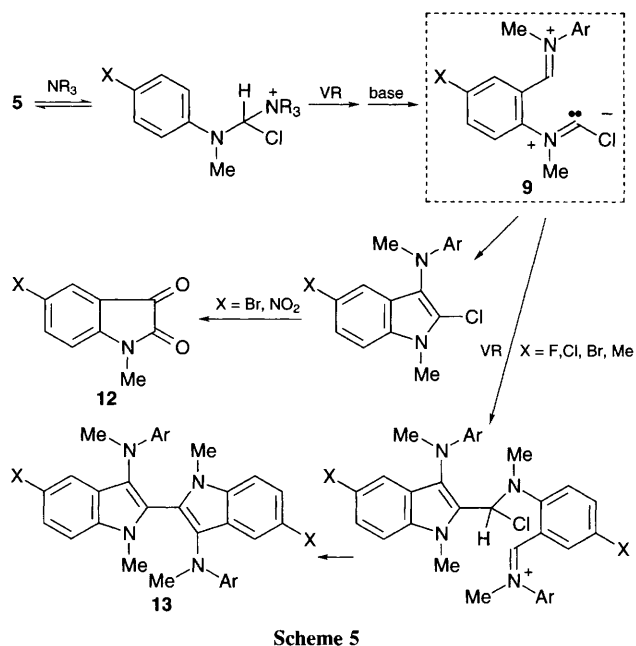
Scheme 4

products is outlined in Scheme 3. Thus formylation of the carbene, now an 'unpoled' Vilsmeier reagent, followed by proton loss leads to the dimer 7. Further ring formylation of this enamic dimer and electrocyclicisation of the resulting triene (in a manner analogous to the formation of quinolinium salts from Vilsmeier formylation of α -chloroenamines³) 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 POCl₃ 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 groups³ but the alkene being activated. From the *p*-nitroformanilide (4, X = NO₂) 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



Scheme 5

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 = NO₂ (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[-], NO₂[-]) for which the structure 13 has been confirmed.§

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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

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- 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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