

Mannich Reactions of Nucleophilic Aromatic Compounds involving Aminals and α -Amino Ethers activated by Chlorosilane Derivatives; Catalysis by Chlorotrimethylsilane

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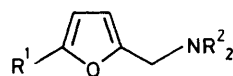
Aminals and α -amino ethers afford *N,N*-dialkylmethyleneammonium salts by reaction with dichloro(dimethyl)- and trichloro(methyl)-silanes, but whereas chlorotrimethylsilane interacts with α -amino ethers to yield iminium salts, the reaction of the latter silane with aminals does not: *in situ* Mannich reactions may be carried out using these systems, and in the case of the reactions using chlorotrimethylsilane and aminals the reactions can be catalytic with respect to the silane.

Although important recent modifications to the experimental methods used in Mannich¹ reactions involve the use of pre-formed methyleneammonium salts,² we have concentrated on reactions carried out in aprotic solvents without the isolation of reactive intermediates. A number of methods have been used to prepare iminium salts and these include reactions of acetyl chloride with bis(dialkyl-amino)methanes (aminals),³ of trifluoroacetic anhydride with *N*-oxides,⁴ and of trichloro(methyl)silane with alkoxy(dialkyl-amino)methanes (α -amino ethers).⁵ We have recently reported *in situ* reactions carried out between aminals or α -amino ethers and nucleophilic aromatic compounds activated by means of acetyl chloride or sulphur dioxide.⁶ We also set ourselves an objective to devise reaction conditions in which strong acids, such as hydrogen chloride, were not produced.

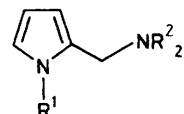
We now report that *in situ* reactions can be carried out using aminals and α -amino ethers in the presence of chlorosilanes and that high concentrations of hydrogen chloride are not involved in reactions of aminals with chlorotrimethylsilane. The reactions using 1 mol. equiv. of chlorosilane were carried out in acetonitrile at room temperature.

Iodotrimethylsilane has been used for the generation of Eschenmoser's salt⁷ (*N,N*-dimethylmethyleneammonium iodide) from bis(dimethylamino)methane.⁸ The preparation

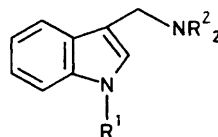
of the analogous chlorides from α -amino ethers using trichloro(methyl)silane⁵ suggested an investigation of *in situ* Mannich reactions using derivatives of silicon tetrachloride. A comparison of the strengths of silicon-oxygen and silicon-nitrogen bonds suggested that it would be profitable to investigate



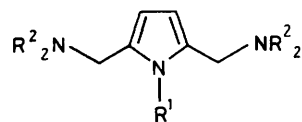
- (1) $R^1 = H$
(2) $R^1 = Me$



- (3) $R^1 = H$
(4) $R^1 = Me$



- (5) $R^1 = H$
(6) $R^1 = Me$



- (7) $R^1 = H$
(8) $R^1 = Me$

Table 1. Reactions of α -amino ethers with heterocycles in the presence of chlorosilanes

Heterocycle	α -Amino ether	Silane	Time (h)	Product(s) ^a	Yield (%) ^b
Furan	EtOCH ₂ N[CH ₂] ₄	Me ₃ SiCl	48	(1; R ² ₂ = [CH ₂] ₄)	52
2-Me-furan	EtOCH ₂ N[CH ₂] ₄	Me ₃ SiCl	48	(2; R ₂ = [CH ₂] ₄)	86
1-Me-pyrrole	EtOCH ₂ NMe ₂	Me ₃ SiCl	24	(4; R ² = Me)	21.5
				+ (8; R ² = Me)	18.5
1-Me-pyrrole	EtOCH ₂ NEt ₂	Me ₃ SiCl	24	(4; R ² = Et)	23
				+ (8; R ² = Et)	49
1-Me-pyrrole	EtOCH ₂ N[CH ₂] ₅	Me ₃ SiCl	24	(4; R ² ₂ = [CH ₂] ₅)	43
				+ (8; R ² ₂ = [CH ₂] ₅)	47
1-Me-pyrrole	EtOCH ₂ NPr ⁱ ₂	MeSiCl ₃	24	(4; R ² = Pr ⁱ)	42
				+ (8; R ² = Pr ⁱ)	28
1-Me-indole	EtOCH ₂ NEt ₂	Me ₃ SiCl	48	(6; R ² = Et)	78

^a All new compounds reported in this communication have been fully characterized by spectroscopic methods and elemental analysis or accurate mass measurement of the molecular ion. ^b Yields based on α -amino ether-heterocycle ratio = 1 : 1.

Table 2. Reactions of amins with heterocycles in the presence of chlorosilanes

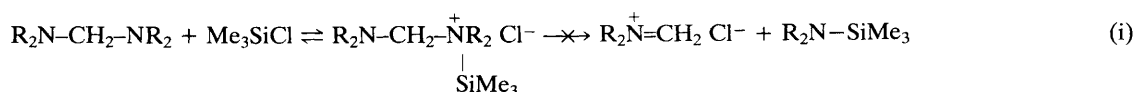
Heterocycle	Aminal	Silane ^a (mol %)	Time (h)	Products	Yield (%) ^b
Furan	[(CH ₂) ₅ N] ₂ CH ₂	MeSiCl ₃ (100)	72	(1; R ² ₂ = [CH ₂] ₅)	15
2-Me-furan	[(CH ₂) ₄ N] ₂ CH ₂	Me ₂ SiCl ₂ (100)	48	(2; R ² ₂ = [CH ₂] ₄)	58
2-Me-furan	[(CH ₂) ₄ N] ₂ CH ₂	Me ₃ SiCl (100)	48	(2; R ² ₂ = [CH ₂] ₄)	0
				+ aminal	51
Pyrrole	(Me ₂ N) ₂ CH ₂	Me ₃ SiCl (100)	48	(3; R ² = Me)	22
				+ (7; R ² = Me)	49
1-Me-pyrrole	[(CH ₂) ₄ N] ₂ CH ₂	MeSiCl ₃ (100)	72	(4; R ² ₂ = [CH ₂] ₄)	75
1-Me-pyrrole	(Me ₂ N) ₂ CH ₂	Me ₂ SiCl ₂ (100)	48	(4; R ² = Me)	59
				+ (8; R ² = Me)	25
1-Me-pyrrole	(Me ₂ N) ₂ CH ₂	Me ₃ SiCl (100)	2	(4; R ² = Me)	20
				+ (8; R ² = Me)	40
1-Me-pyrrole	[(CH ₂) ₄ N] ₂ CH ₂	Me ₃ SiCl (100)	118	(8; R ² ₂ = [CH ₂] ₄)	70
1-Me-pyrrole	[(CH ₂) ₄ N] ₂ CH ₂	Me ₃ SiCl (5)	24	(4; R ² ₂ = [CH ₂] ₄)	17
				+ (8; R ² ₂ = [CH ₂] ₄)	61
1-Me-pyrrole	(Me ₂ N) ₂ CH ₂	Me ₃ SiCl (5)	24	(8; R = Me)	63
1-Me-pyrrole	(Et ₂ N) ₂ CH ₂	Me ₃ SiCl (12.5)	24	(8; R = Et)	78
1-Me-pyrrole	[(CH ₂) ₅ N] ₂ CH ₂	Me ₃ SiCl (12.5)	24	(4; R ² ₂ = [CH ₂] ₅)	38
				+ (8; R ² ₂ = [CH ₂] ₅)	46
Indole	(Me ₂ N) ₂ CH ₂	Me ₃ SiCl (100)	48	(5; R = Me)	63
1-Me-indole	(Me ₂ N) ₂ CH ₂	Me ₃ SiCl (100)	48	(6; R = Me)	59

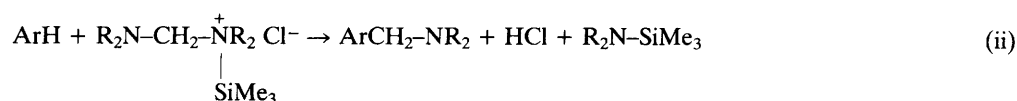
^a 100 mol % at room temperature and using catalytic amounts under reflux. ^b Yields based on aminal-heterocycle ratio = 1 : 1.

reactions using both amins and α -amino ethers. ¹³C N.m.r. spectroscopy indicated that methyleneammonium salts are also formed when solutions of α -amino ethers in deuterio-acetonitrile-sulphur dioxide are treated with dichloro-(dimethyl)- or chloro(trimethyl)-silanes. The methylene carbon signal is typically observed as a triplet in the broad band ¹H-decoupled spectrum. For example, we found that when a solution of ethoxy(diethylamino)methane in deuterio-acetonitrile-sulphur dioxide was treated with 1 mol. equiv. of dichloro(dimethyl)silane, the broad-band decoupled ¹³C n.m.r. spectrum was immediately changed and showed three resonances at δ_C 12.5 (s), 55.0 (t, *J* 3.5 Hz), and 165.4 (t, *J* 13.5 Hz). On the other hand, we were unable to detect iminium salts when amins were treated with chlorotrimethylsilane. The addition of 1 mol. equiv. of, for example, *N*-methylpyrrole to the n.m.r. solutions quickly resulted in the appearance of absorptions due to 1-methyl-2-(dialkylamino)methylpyrrole, even in the case of mixtures of amins and chlorotrimethylsilane. Preparative-scale reac-

tions resulting in the formation of 2-dialkylaminomethyl derivatives of furan (1), 2-methylfuran (2), pyrrole (3), 1-methylpyrrole (4), 3-dialkylaminomethyl derivatives of indole (5) and 1-methylindole (6), and 2,5-bis(dialkylaminomethyl) derivatives of pyrrole (7) and 1-methylpyrrole (8) are reported in Tables 1 and 2.

We believe that the most significant results reported are those using 2-methylfuran and those involving 1-methylpyrrole in reactions of amins with chlorotrimethylsilane. Our results show that 2-methylfuran only affords Mannich bases in reactions that proceed by way of iminium salts. This substrate therefore allows us to establish that a number of mechanisms can operate in reactions involving chlorosilanes. In particular iminium salts are not involved in the reactions of amins with chlorotrimethylsilane. Evidently chlorotrimethylsilane interacts with amins to form a low equilibrium concentration of quaternary silylammonium salts which do not break down to iminium salts [reaction (i)].





The significant observation in reactions of 1-methylpyrrole with amins that are activated by chlorotrimethylsilane is the rapid formation of the 2,5-disubstituted products (Table 2), whereas reactions involving iminium chlorides afford predominantly the mono substitution products. We presume that the hydrochlorides of the monosubstitution products are less nucleophilic than the starting material, but that the free Mannich bases are significantly more reactive than the starting material. We conclude, therefore, that in the reactions involving chlorotrimethylsilane a build-up of free hydrogen chloride does not occur. It is known that the majority of quaternary silylammonium salts are unstable;⁹ exceptions involve non-nucleophilic counter ions such as [Co(CO)₄]⁻.¹⁰ The removal of the hydrogen chloride formed in the Mannich reaction must involve the regeneration of chlorotrimethylsilane [reaction (iii)].

It follows that the reactions of the amins with chlorotrimethylsilane should be catalytic with respect to the latter. Experiment confirms this conclusion. Although our early results were inconclusive we found that, for example, the reaction of 1-methylpyrrole with dipyrrolidin-1-ylmethane carried out using 5 mol % of chlorotrimethylsilane under reflux in acetonitrile gave a mixture of 1-methyl-2-(pyrrolidin-1-methyl)pyrrole (17%) and 1-methyl-2,5-di(pyrrolidin-1-ylmethyl)pyrrole (61%). A number of other examples of the catalytic effect are given in Table 2.

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