

Condensation of *N,N*-Bis(trimethylsilyl)formamide with Aldehydes: a General Method for the Synthesis of 1-Formamido-1-trimethylsilyloxyalkanes

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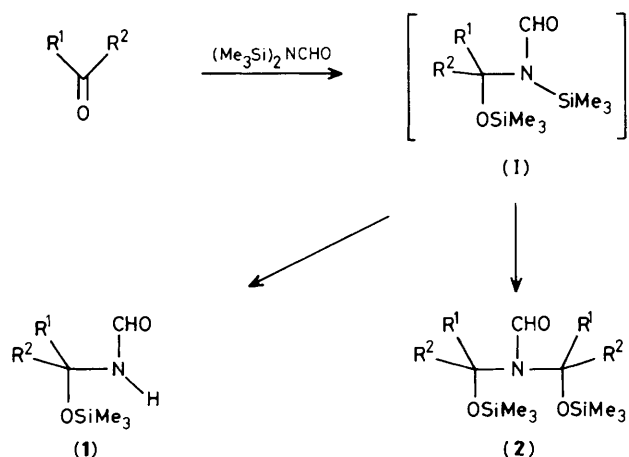
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Reaction of bis(trimethylsilyl)formamide with simple aldehydes gives 1-formamido-1-trimethylsilyloxyalkanes (and the corresponding adducts with ketones), which undergo displacement of trimethylsilanol by a variety of nucleophiles to give α -substituted amides.

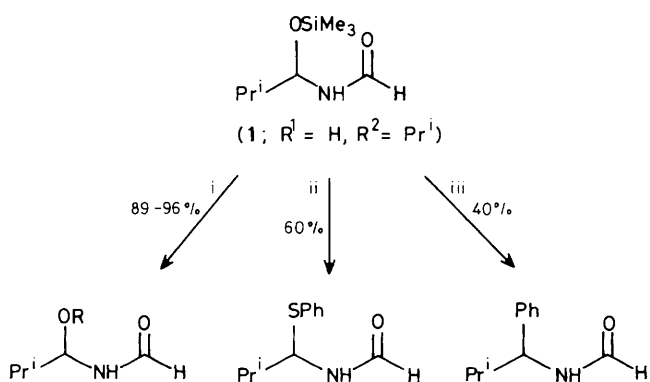
N-Acylimines and *N*-acyliminium salts are versatile synthetic intermediates which undergo synthetically useful reactions with nucleophiles,¹ dienes,² and dienophiles.³ However, in most cases, they are too unstable to be stored for any length of time and must be generated *in situ*. We report a convenient preparation of a new type of *N*-acylimine precursor.

Hitherto the most widely used *N*-acylimine precursors have been α -(*N*-acylamino) ethers (prepared by electrochemical oxidation of an amide in the presence of an alcohol⁴) and

α -(*N*-acylamino)alcohols. Individual examples of the latter species have been prepared by the reduction of a cyclic imide⁵ or by the acid-catalysed addition of an amide to an especially reactive aldehyde,^{1a} such as formaldehyde or ethyl glyoxylate. However, these procedures are not generally applicable to the synthesis of α -(*N*-acylamino)alcohols because, in the absence of specific stabilising factors, they show a marked tendency to revert back to the corresponding aldehyde (or ketone) and amide.⁶



Scheme 1



Scheme 2. i, ROH (R = Me, Et), 2-4% CF₃SO₃SiMe₃, 10 min; ii, PhSH, CCl₄, 5% CF₃SO₃SiMe₃, 30 min; iii, PhMgBr, diethyl ether, 4 h.

Table 1. Formation of formamidotrimethylsilyloxyalkanes (**1**) from aldehydes and ketones.^a

Carbonyl compound	BSF/equiv.	Conditions ^b	Time/h	% Yield	M.p. or b.p. of adduct
n-Butyraldehyde	1.3		144	78	B.p. 98—100°C/0.3 mm
	5.1	Cat.	1	63	
Isobutyraldehyde	1.4		17	48	B.p. 73—80°C/0.3 mmHg
	3.4	Cat.	2	93	
Pivalaldehyde	1.7		120	6	M.p. 55—57°C
	1.6	Cat.	20	85	
Phenylacetaldehyde ^c	2.5	Cat.	1	97	M.p. 82—83°C
Benzaldehyde	5.4	Cat.	8	93 ^d	
Crotonaldehyde	3.9	Cat.	21	40 ^d	
Methyl pyruvate	3.5	Cat.	21	83	M.p. 91—92°C
Acetone	2.9	Cat.	168	38 ^d	

^a All new compounds gave expected i.r., ¹H n.m.r., and mass spectra. Correct microanalyses were obtained for all crystalline compounds and the oils which could be distilled. ^b Reflux in CCl₄ or CHCl₃ unless otherwise indicated. Cat., room temperature in CCl₄ or CHCl₃ with 1—5 mol % CF₃SO₃SiMe₃. ^c Under thermal conditions the silylenol ether was produced. ^d These adducts decomposed on attempted distillation.

The reagent bis(trimethylsilyl)formamide (BSF)⁷ has been shown to be a silylating agent,⁸ to undergo nucleophilic attack at the carbonyl group,⁹ and to behave as an *N*-nucleophile.^{9a,10} We now report that BSF reacts with simple aldehydes to give 1-formamido-1-trimethylsilyloxyalkanes (**1**; R¹ = H, R² = alkyl) and the corresponding adducts with ketones (**1**; R¹, R² = alkyl)[†] (Scheme 1) which may be purified by flash chromatography on silica, followed by distillation or recrystallisation. In most cases these adducts show some decomposition over a period of months at room temperature but may be conveniently stored without decomposition at lower temperatures.

In our early experiments the adducts were formed by reflux of BSF and the aldehyde in tetrachloromethane or chloroform over several days. Under these conditions, phenylacetaldehyde did not undergo the normal addition reaction, but instead was converted into the corresponding trimethylsilylenol ether. More recently we have discovered that the addition reaction is markedly catalysed by trimethylsilyl trifluoromethanesulphonate (CF₃SO₃SiMe₃) and normally goes to completion within a few hours at room temperature (Table 1). Under these conditions, even phenylacetaldehyde is converted in high yield into the corresponding adduct (**1**). In some cases the catalytic procedure resulted in the formation of *N,N*-bis(1-trimethylsilyloxyalkane)formamides (**2**; R¹ = H, R² = alkyl) in addition to the expected 1:1 adducts (**1**), but we have found that bis adduct formation can be minimised by using an excess of BSF over the aldehyde (Table 1). The addition to simple ketones, such as acetone, requires longer reaction times (up to a week) and gives poor yields. In a representative experiment: to a stirred solution of BSF (3 ml, 14.0 mmol, 3.4 equiv.) and CF₃SO₃SiMe₃ (0.15 ml of a 0.52 M solution in CCl₄, 0.078 mmol, 2 mol %) in dry CCl₄ (16 ml) under nitrogen, at room temperature, isobutyraldehyde (0.40 ml, 4.1 mmol) was added dropwise. After 2 h the solution was evaporated to dryness and chromatographed on flash silica gel. Elution with diethyl ether gave 1-formamido-1-trimethylsilyloxy-2-methylpropane (720 mg, 93%) as a colourless oil.

As expected, the monoadducts (**1**; R¹ = H, R² = alkyl) generated by this procedure undergo ready substitution of the trimethylsilyloxy group by a variety of nucleophiles including Grignard reagents (see Scheme 2). The product from the

reaction with thiophenol is especially interesting because of the well established utility of such compounds as precursors of free radical intermediates.¹¹

BSF has been found to react with simple aldehydes to give 1-formamido-1-trimethylsilyloxyalkanes (and the corresponding adducts with ketones) in high yields, at room temperature, with CF₃SO₃SiMe₃ as catalyst; these compounds undergo substitution at the α -carbon with phenylmagnesium bromide and heteroatom nucleophiles.

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[†] ¹H N.m.r. studies show the initially formed adduct to be (I) which is spontaneously converted into (**1**) on silica gel chromatography.