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(Polyfluoro)silane-mediated generation of azomethine ylides from imines and their cycloaddition leading to *N*-heterocycles

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Abstract—The novel generation and cycloaddition of azomethine ylides from an α-(trimethylsilyl)imine using (polyfluoro)silanes is described. The method was successfully applied to an efficient one-pot process. Namely, an azaallyl anion, generated by abstraction of the hydrogen α to an imino nitrogen, was treated with a di- or trifluorosilane to give an azomethine ylide intermediate below room temperature. The generated 1,3-dipole was smoothly trapped with dipolarophiles to afford nitrogen-containing five-membered heterocycles in good yields. © 2003 Elsevier Science Ltd. All rights reserved.

1,3-Dipolar cycloaddition reactions constitute a powerful route to the construction of a variety of five-membered heterocycles.[1] Of the various 1,3-dipoles available for this reaction, an azomethine ylide is one of the most important, in that it can be used in the synthesis of *N*-heterocycles. As a result, a number of investigators have reported on methods for generating azomethine ylides.[2] There are some examples of methods in which the characteristics of silicon are utilized in the generation of dipoles from α-silylimine derivatives. These methods enable the generation of less-stabilized azomethine ylides by taking advantage of the fact that carbon–silicon bonds are readily cleaved by nucleophiles including fluoride ion. Thus, the desilylation of α-silyliminium salts,[3a–h] the treatment of α-silylimine derivatives with an acyl halide,[3i–k] trimethylsilyl triflate[3l,3m] or acids,[3n,3o] the water-induced desilylation of α-silylimines,[3p–s] and desilylation of ketene acetal[3t,3u] have been developed to date. Among these, the unique protodesilylation of (2-azaallyl)silanes leading to the formation of *N*-unsubstituted azomethine ylides was reported by Pearson and coworkers.[3o] On the other hand, in our earlier papers, we reported that azomethine ylides can be generated from *N*-(silylmethyl)imines[4a,b,e] or *N*-(silylmethyl)amides[4c] through an intramolecular silatropic rearrangement and from α-silylimidates[4d] using F_3SiPh or $F_2SiMePh$ as a quaternization–desilylation reagent. With these facts in mind, we report on a novel and unique strategy for the catalytic generation of azomethine ylides from imines based on the fluorosilane-mediated generation of an azomethine ylide from an α-silylimine.[5]

The generation of an azomethine ylide mediated by (polyfluoro)silanes from an α-silylimine and its cycloaddition were first examined as listed in Table 1. When *N*-(α-trimethylsilylbenzyl)benzylideneamine (**1**)[6] was treated with 2 equiv. of *N*-phenylmaleimide (NPMI) in the presence of dimethylphenylfluorosilane (1.2 equiv.) in benzene at room temperature for 24 h, the expected reaction did not proceed and the starting imine was recovered (run 1). Although the use of a difluorosilane ($F_2SiPhMe$) led to the desired reaction, affording cycloadducts in moderate yields as a mixture of stereoisomers (run 2), a trifluorosilane (F_3SiPh) was found to be a superior reagent for the present purpose (run 3). It is noteworthy that cycloaddition was achieved even in the presence of a catalytic amount of F_3SiPh (run 4). Although these results indicate that trifluorosilane is a good mediator for generation of the azomethine ylide (especially, in the step of an α-silylimine), further investigation is necessary to improve the reaction efficiency under catalytic conditions.

In an attempt to overcome the problem concerning the catalytic reaction, we propose an alternative method for generating azomethine ylides mediated by (polyfluoro)silanes as outlined in Scheme 1, which is mechanistically rationalized as follows. The abstraction of the hydrogen α to the imino nitrogen of the starting imine is accomplished by LDA, followed by the addition of (polyfluoro)silanes, to give α-fluorosilylimines.

Keywords: azomethine ylide; 1,3-dipolar cycloaddition; fluorosilane; α-silylimine; pyrrolidine.

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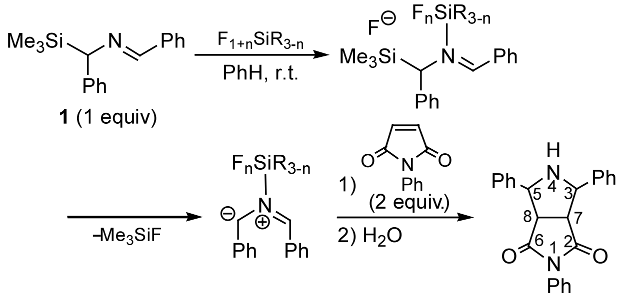
Table 1. Generation of *N*-silylated azomethine ylides and their cycloaddition with *N*-phenylmaleimide (NPMI) from an α-silylimine using fluorosilanes[a]



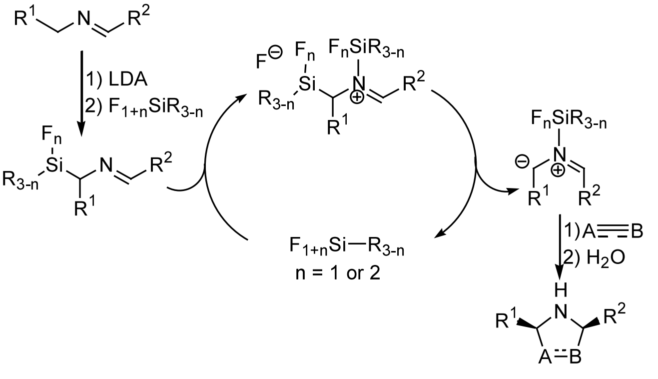
Run	Fluorosilane (equiv.)	Time (h)	Yield (%)	(3,5-*cis*[b]: 3,5-*trans*)
1	$FSiMe_2Ph$ (1.2)	24	0	–
2	$F_2SiMePh$ (1.2)	24	47[c]	(70:30)
3	F_3SiPh (1.2)	24	98	(74:26)
4	F_3SiPh (0.2)	48	41[d]	(73:27)

[a] Reaction conditions: **1** (1 mmol), NPMI (2 mmol), fluorosilane (0.2–1.2 mmol), in PhH (4 mL) at rt, 24–48 h.

[b] *Endo*:*exo* = ca. 40:60.

[c] Recovery of **1**: 45%.

[d] Recovery of **1**: 53%.



Scheme 1.

The free (polyfluoro)silane at this stage acts as a mediator for the generation of azomethine ylides from α-(fluorosilyl)imines. The ylides react smoothly with dipolarophiles to afford the initial cycloadducts, the N–Si bond of which is cleaved by water during the workup process.

On the basis of the concept, we investigated the in situ formation of α-fluorosilylated imines, which might be more readily desilylated by F^- because of their electron-withdrawing substituents (fluorine atoms) on the silyl group, and their conversion to azomethine ylides mediated by (polyfluoro)silane (Table 2). An azaallyl anion, generated from *N*-benzylidene-*N*-benzylamine (**2**) and LDA, was reacted with 2 equiv. of difluorosilane ($F_2SiMePh$), followed by treatment with NPMI (3 equiv.) to afford the corresponding cycloadducts in high yield as a mixture of stereoisomers. Monitoring of the reaction by ^1H NMR (in d_8-THF) at −78°C to room temperature confirmed the nearly quantitative formation of the α-fluorosilylated imine. The NMR study indicated that only 1 equiv. of $F_2SiMePh$ was required to produce the α-fluorosilylimine. When $F_2SiMePh$ (1.1 equiv.) was employed in the reaction (1 equiv. for formation of the imine and 0.1 for the generation of the ylide), the catalytic cycloaddition proceeded in good yield. A trifluorosilane (F_3SiPh) was found to be a more efficient mediator in the present reaction, giving the desired products in high yield. When dimethyl fumarate was used as a dipolarophile in the presence of 1.2 equiv. of F_3SiPh under the same conditions, the corresponding cycloadducts were obtained in good yields. Although the use of a stoichiometric amount of $F_2SiMePh$ gave good results in the case of dimethyl maleate, catalytic cycloaddition was also realized. The use of *N*-benzylidene-*N*-methylamine as a dipolarophile was successful in the cycloaddition and imidazolidines were obtained in good yields. It is noteworthy that the present method was found to be applicable to the generation of less-stabilized azomethine ylides which do not bear ylide-stabilizing substituents on each carbon. In particular, the cycloaddition of *N*-neopentylidene-*N*-benzylamine as the starting imine proceeded efficiently and involved the catalytic generation of a less-stabilized azomethine ylide.

In summary, this represents the first description of the catalytic generation of azomethine ylides from imines including less-stabilized ylides using (polyfluoro)silanes under extremely mild conditions. The 1,3-dipoles were successfully trapped with dipolarophiles to afford five-membered heterocycles in good yields. The present reaction proceeds in a one-pot system: the (polyfluoro)silanes play multiple functions as a reagent for (1) the silylation of the starting imines, (2) quaternization of the α-(fluorosilyl)imines generated in situ, (3) desilylation of the species formed in (2), and (4) a catalyst for the generation of azomethine ylides. We are currently investigating the mechanism of this reaction including the stereochemistry, in more detail, as well as applications to the synthesis of other *N*-heterocycles.

Acknowledgements

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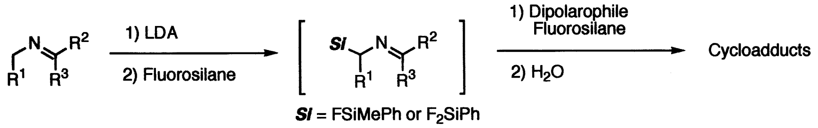
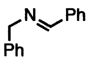
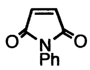
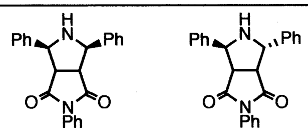
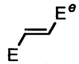
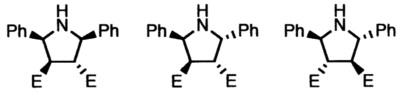
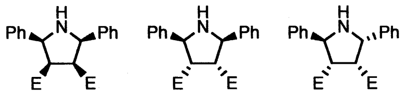
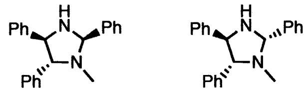
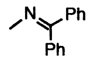
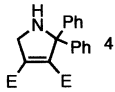
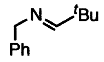
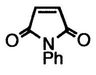
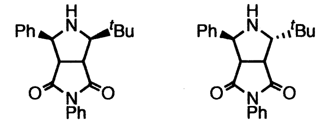
Table 2. Generation of *N*-silylated azomethine ylides from imines using fluorosilanes and their cycloaddition with dipolarophiles[a]



Imine	Dipolarophile (equiv.)	Fluorosilane (equiv.)	Cycloadducts Yield (ratio)
 2	 (3.0)		
		$F_2SiMePh$ (2.0)	90% (90[b] : 10)
		(1.1)	50%[c] (90[b] : 10)
		F_3SiPh (1.2)	87%[d] (69[b] : 31)
2	 (1.2)	F_3SiPh (1.2)	
			83% (75 : 18 : 7)
2	 (3.0)		
		F_3SiPh (1.2)	46% (78 : 22 : 0)
		$F_2SiMePh$ (2.0)	75% (83 : 8 : 9)
2	 (3.0)	$F_2SiMePh$ (2.0)	
			71% (14 : 86)
	E—≡—E[e] (2.1)	$F_2SiMePh$ (2.0)	 41%
	 (1.2)	F_3SiPh (1.1)	
			63% (76[f] : 24[g])

[a] Reaction conditions: imine (6 mmol), LDA (6.5 mmol), fluorosilane (6.6 - 12 mmol), in THF (10 mL) at -78 °C to 0 °C, 1 h, dipolarophile (7.2 -18 mmol) in THF (16 mL) at 0 °C to r.t., overnight. [b] *endo* : *exo* = ca. 50 : 50. [c] Recovery of **2**: 24%. [d] Recovery of **2**: 12%. [e] E: $-CO_2Me$. [f] All *cis* : 3,7-*trans*-5,8-*trans* = 48 : 52. [g] 3,7-*cis*-5,8-*trans* : 3,7-*trans*-5,8-*cis* = 60 : 40.

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