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Preparation of Enamines by the Reaction of Ketones and Secondary Amines with Silylating Agents

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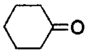
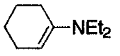
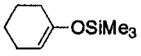
1. Introduction

Enamines are useful intermediates in organic synthesis, and many methods for their preparation have been developed.[1] Of these protocols, the azeotropic removal of water in benzene or toluene[2] is the most common, though methods using molecular sieves,[3] $TiCl_4$,[4] and metal amides[5] have also been reported. Franck and Weinreb were the first to report the use of *N*-silylamines for the preparation of enamines from aldehydes and ketones.[6] While this method is convenient, it suffers from requiring 2 equiv of the silylamine to drive the reaction to completion.

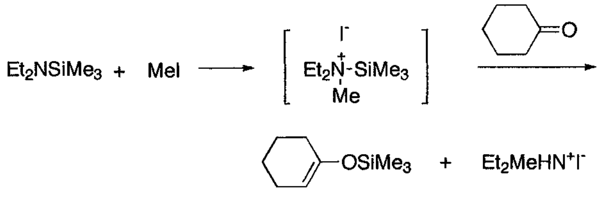
Previously we have reported that an equimolar mixture of silylamine and methyl iodide reacts with ketones much like trimethylsilyl iodide to generate silyl enol ethers.[7] While studying this reaction in detail, we observed enamine formation as a competitive process when less than 1 equiv of methyl iodide was used (see Table 1). From a mechanistic standpoint, we believe that reaction of methyl iodide with the silylamine generates an active silylating adduct that transfers a TMS group to the ketone. When 1 equiv of MeI is used, the amount of active adduct is sufficient to consume all of the starting ketone. However, when less than 1 equiv of MeI is used, the silyl enol ether is generated first, corresponding to the amount of used methyl iodide. Then residual silylamine reacts with ketone to give enamine according to the scheme reported by Franck and Weinreb. The product distribution is a function of the amount of MeI employed, and when a catalytic amount is used, enamine formation is almost exclusive.

Table 1. Relationship between the Amount of MeI and the Product Ratio

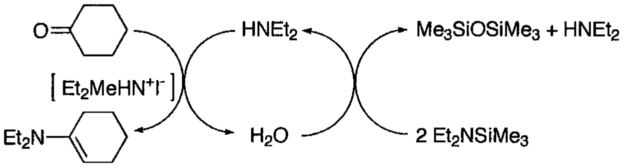
Molar ratio of starting materials			Product ratio[a]	
	Me_3SiNEt_2	MeI		
1	1	1	--	1
1	1	0.5	1	2
1	1	0.05	9.5	1

[a] Product ratio was estimated by GC.

Scheme 1



Scheme 2



In this paper, we disclose a method that uses *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and a catalytic amount of methyl iodide for the preparation of enamines from ketones.

2. Results and Discussion

On the basis of previous reports[5] and our own results,[7] we anticipated that an appropriate silylating agent bearing two transferable silyl groups on a moiety that would be inert to the ketone substrate should eliminate the need for *N*-silylamines as a starting material. *N*,*O*-Bis(trimethylsilyl)acetamide fulfills this requirement.[8] When cyclopentanone was added to a solution of pyrrolidine and methyl iodide in benzene followed by the addition of BSA, enamine formation proceeded uneventfully (Table 2, entry 1a). Encouraged by these results, we further explored the scope of this reaction.

Our results are summarized in Table 2. The yields of enamine are good to excellent, and the reaction is general for cyclic and acyclic ketones, though it appears to be

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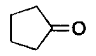
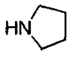
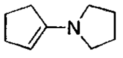
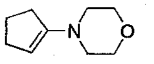
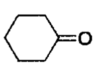
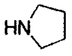
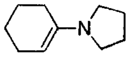
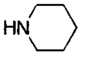
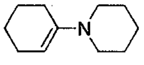
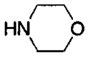
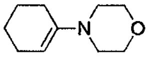
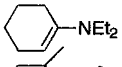
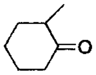
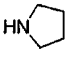
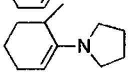
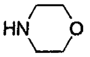
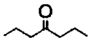
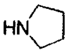
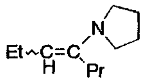
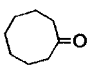
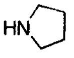
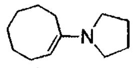
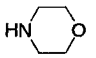
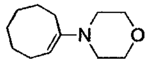
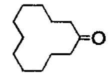
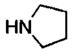
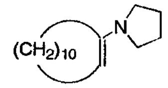
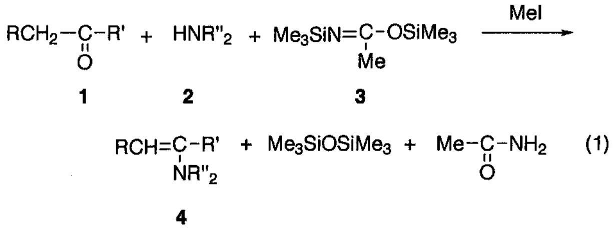
Table 2. Preparation of Enamines Using BSA as a Dehydrating Agent

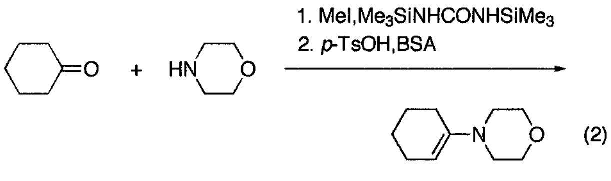
entry	ketone	amine	solvent	reacn[a] temp (°C)	reacn time (h)	enamine	yield (%)
1a			petroleum ether	40 - 50	1.5		82
1b			petroleum ether	35 - 45	1.5		89
2a			petroleum ether	45 - 50	3.5		92
2b			petroleum ether	35 - 45	3.5		80
2c			petroleum ether	40 - 50	1.5		91
2d		HNEt₂	benzene	65 - 75	6.5		88
3a			petroleum ether	35 - 45	2		85[b]
3b			benzene	65 - 90	8	no reaction	- -
3c		HNEt₂	benzene	80 - 90	15	no reaction	- -
4			petroleum ether	40 - 50	2.5		85
5a			benzene	30 - 40	1		85
5b			benzene	80 - 90	5		93
6			benzene	30 - 40	3		92

[a] Reaction time includes the addition time of BSA. [b] 1-Pyrrolidino-2-methylcyclohexene was not detected by GC–MS and ^{13}C NMR.

sensitive to steric interactions (Table 2, entries 3b,c). Furthermore, a variety of enamines can be prepared by this method, though in general pyrrolidine appears to be the most reactive amine (Table 2, entry 3a vs 3b,c and note that the pyrrolidine reactions always proceed at 30–50 °C).



$$\underset{\mathbf{1}}{RCH_2-\underset{\underset{O}{\|}}{C}-R'} + \underset{\mathbf{2}}{HNR''_2} + \underset{\mathbf{3}}{Me_3SiN=\underset{\underset{Me}{|}}{C}-OSiMe_3} \xrightarrow{MeI} \underset{\mathbf{4}}{RCH=\underset{\underset{NR''_2}{|}}{C}-R'} + Me_3SiOSiMe_3 + Me-\underset{\underset{O}{\|}}{C}-NH_2 \quad (1)$$



(2)

1. yield 90%
2. yield 84%

Not surprisingly, the reaction is not limited to BSA. Bis(trimethylsilyl)urea was equally effective as the silylating agent, affording the morpholine enamine of cyclohexanone in 90% yield (eq 2). Finally, *p*-toluensulfonic acid can be used in place of methyl iodide with no appreciable loss in effectiveness (eq 2).

3. Experimental Section

General Remarks. Commercially available BSA, bis(trimethylsilyl)urea, amines, ketones, petroleum ether, benzene, and methyl iodide were used without purification. The structure of enamines was confirmed by comparison of the spectral data with those described in the literature.[2–6,9]

Illustrative Procedure for the Preparation of Enamines. In a four-necked flask, equipped with a mechanical stirrer, a condenser, a thermometer, and a dropping funnel was placed 41.8 g (0.48 mol) of morpholine, 1.7 g of methyl iodide (0.012 mol), and 100 mL of petroleum ether, and the mixture was heated at 40–50 °C for 0.5 h. To this solution was added 33.6 g (0.4 mol) of cyclopentanone, followed by the addition of 81.2 g (0.4 mol) of BSA over a period of 0.5 h. The mixture was stirred at 70–80 °C for 1 h, until the ketone was consumed, as shown by gas chromatography. After the addition of 100 mL of petroleum ether, the reaction mixture was cooled in an ice water bath. After the precipitated acetamide was separated by filtration, the volatile materials were evaporated.[10] The residue was fractionally distilled to give 54.5 g (89%) of 1-morpholinocyclopentene, bp 80–81 °C/3 Torr. The IR spectrum was identical with an authentic spectrum:[9j] IR (KBr) 3070, 1630 cm^{-1}; ^{1}H NMR (C_6D_6, 60 MHz) δ 1.47–2.13 (m, 2H), 1.90–2.50 (m, 4H), 2.50–2.90 (m, 4H), 3.10–3.83 (m, 4H), 4.47 (t, J = 3 Hz, 1H).

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[10] When using benzene as solvent, the reaction mixture was evaporated under reduced pressure and the residue was mixed with petroleum ether in order to efficiently separate the precipitated acetamide.