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A Convenient Synthesis of β-Aminoesters. The Reaction of Imines with Ketene Silyl Acetals Catalyzed by Phosphonium Salts

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In the presence of a catalytic amount of a diphosphonium salt, the reaction of various imines, including 2-[N-(diphenylmethyl)formimidoyl]-pyridine, with ketene silyl acetals proceeded smoothly to afford the corresponding β-aminoesters in good yields.

The reaction of imines with ketene silyl acetals forming β-aminoesters, frequently employed as useful intermediates in the synthesis of β-lactams, has been carried out by the use of an equimolar amount of Lewis acid such as $TiCl_4$.1) However, there have been reported no examples on the same reaction performed by using a catalytic amount of promoter. In the previous paper,2) we have reported that in the presence of phosphonium salts as catalysts, the aldol-type reaction of aldehydes or acetals with several nucleophiles and the Michael reaction of α,β-unsaturated ketones or acetals with silyl nucleophiles took place smoothly to give the corresponding adducts in good yields. In the continuing study, we found that the reaction of 4-dimethylaminobenzaldehyde with t-butyldimethylsilyl ketene acetal proceeded smoothly by the use of a catalytic amount of a diphosphonium salt different from the Lewis acid mediated reactions in which Lewis acids such as $TiCl_4$, $SnCl_4$ are neutralized by the amine. So, we further studied on the synthesis of various β-aminoesters from imines and ketene silyl acetals by the use of diphosphonium salts (1 and 2) as catalysts.

$$R_3\overset{+}{P}\text{-O-}\overset{+}{P}R_3\,(CF_3SO_3^{-})_2 \qquad \begin{array}{rl} R = Bu & \underline{1}^{\,2)} \\ Ph & \underline{2}^{\,3)} \end{array}$$

First, several reaction conditions were screened by taking the reaction of N-benzylideneaniline (3) with ketene silyl acetal of methyl isobutyrate (4) as a model (Table 1). By using a slight excess amount (1.25-1.5 equiv.) of the ketene silyl acetal, the corresponding β-aminoester was obtained in excellent yield (Table 1, entries 3, 4) even when 2.5 mol% of diphosphonium salt 1 was employed as a catalyst.

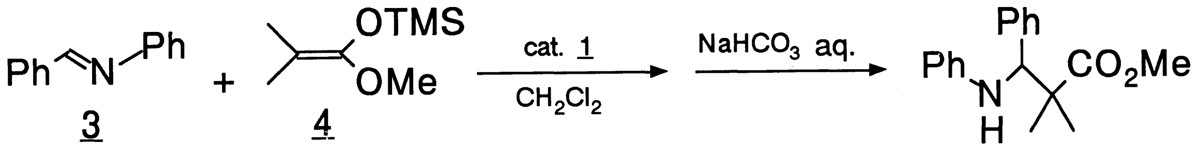


Table 1. The Effects of Molar Ratio and Solvent on the Yield

Entry	Imine/equiv.	Ketene silyl acetal/equiv.	Cat.1/equiv.	Solvent	Temp/°C	Yield/%
1	1.0	1.0	0.07	CH_2Cl_2	-78	80
2	1.5	1.0	0.07	CH_2Cl_2	-78	80
3	1.0	1.25	0.07	CH_2Cl_2	-78	94
4	1.0	1.5	0.07	CH_2Cl_2	-78	quant.
5	1.0	1.5	0.025	CH_2Cl_2	-78	98
6	1.0	1.0	0.07	THF	-78	44
7	1.0	1.0	0.07	toluene	-78	52
8	1.0	1.0	0.07	CH_3CN	-23	75

Several examples for the reaction of imines with ketene silyl acetals are demonstrated in Table 2. In most cases, the reactions with various imines, including 2-[N-(diphenylmethyl)formimidoyl]-pyridine (Table 2, entry 12), proceeded smoothly under mild conditions and the corresponding β-aminoesters were obtained in good yields.

It is noted that trimethylsilyl ketene acetals are more reactive compared with t-butyldimethylsilyl ketene acetals indicating important role of substituents of silicon of the enolates on reactivities. Further, it was shown that a wide variety of solvents such as dichloromethane, toluene, acetonitrile and tetrahydrofuran are available in the present reaction.

A typical procedure is as follows; a solution of diphosphonium salt 1 (7 mol%, 0.021 mmol) in dichloromethane (0.75 ml) was stirred at -78 °C. A mixture of N-benzylideneaniline (3, 0.30 mmol) and ketene silyl acetal of methyl isobutyrate

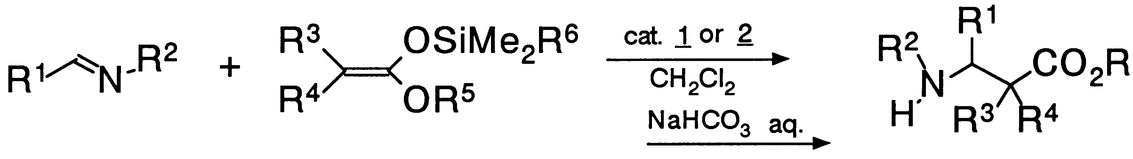
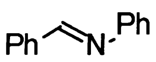
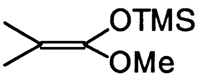
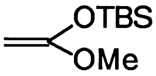
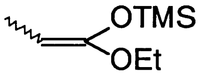
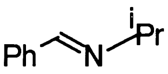
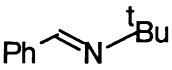
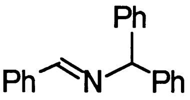
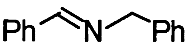
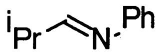
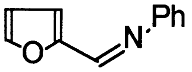
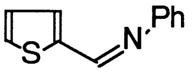
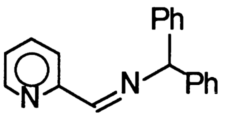


Table 2. The Reaction of Imines with Ketene Silyl Acetals[a]

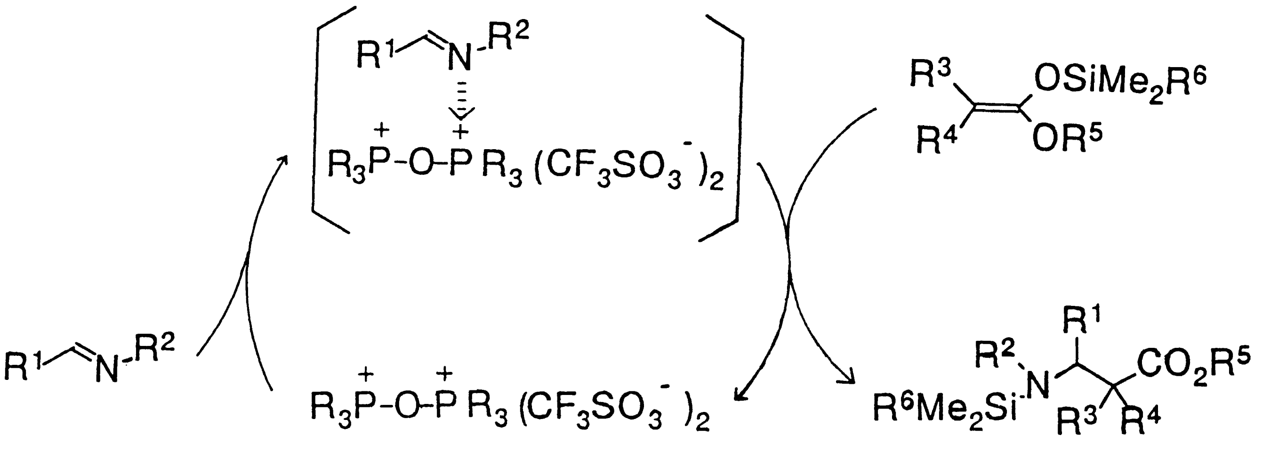
Entry	Imine	Ketene silyl acetal	Cat.	Temp / °C	Time / h	Yield / %
1	 3	 4	1	-78	21	94
2	3		1	-78	16	60
3	3	 (5)	1	-78	6.5	95 [b]
4	3	5	2	-78	6.5	quant. [b]
5		4	1	-78 - 0	20	67
6		4	1	r.t.	23	29
7		4	1	-78	20	67
8		4	1	-78 - r.t.	16	54
9		4	1	-23 - r.t.	17	70
10		4	1	-78	0.5	87
11		4	1	-78	6	71
12		4	1	-78	3.5	97

a) imine : ketene silyl acetal : catalyst = 1 : 1.25 : 0.07.
All products gave satisfactory IR and ^{1}H NMR spectral data.

b) syn : anti = 5 : 3. Determined by ^{1}H NMR.

(4, 0.375 mmol) in dichloromethane (1.5 ml) was added to the above solution. After stirring for 21 h at -78 °C, aqueous solution of sodium hydrogen carbonate was added. The mixture was extracted with dichloromethane and the organic layer was dried with magnesium sulfate. After the solvent was removed under reduced pressure, the residue was purified by preparative thin layer chromatography on silica gel to give the corresponding β-aminoester in 94% yield.

It is assumed that the reaction would proceed by the activation of imines by way of coordination to the diphosphonium salt as shown Scheme 1. The activated imines are in turn attached by nucleophiles as ketene silyl acetals to form silylated β-aminoesters along with regeneration of the diphosphonium salt.



Scheme 1.

Thus, it was shown that β-aminoesters are synthesized in good yields from various imines and ketene silyl acetals by the use of a catalytic amount of the diphosphonium salt.

References

1) I. Ojima, S. Inaba, and K. Yoshida, Tetrahedron Lett., 1977, 3643 ; I. Ojima, S. Inaba, and M. Nagai, Synthesis, 1981, 545; T. Shono, K. Tsubata, and N. Okinaga, J. Org. Chem., 49, 1056 (1984).

2) T. Mukaiyama, S. Matsui, and K. Kashiwagi, Chem. Lett., 1989, 993.

3) D. Crich and H. Dyker, Tetrahedron Lett., 30, 475 (1989).

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