The Reaction of β-Amino Conjugated Enones with Trimethylchlorosilane

Choji Kashima and Yasuhiro Yamamoto*

Department of Chemistry, University of Tsukuba, Sakura-mura, Niihari-gun, Ibaraki 305, Japan

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By the reaction of β-amino conjugated enones with trimethylchlorosilane, both amino acetophenone and pyridine derivatives were formed in good yield. The selectivity of the formation of the products depended on the bulkiness of the *N*-substituents of β-amino conjugated enones.

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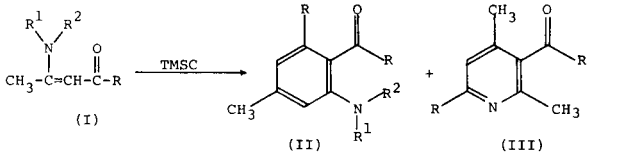
β-Amino conjugated enones have various properties and reactivities owing to three functional groups (1). As a nucleophile, β-amino conjugated enones have three reaction sites, amino nitrogen, α-carbon and carbonyl oxygen. In the case of acylation above 60°, α-acylated β-amino conjugated enones are given (2). However, *N*-acylated derivatives are predominantly obtained by the treatment with acyl chloride below room temperature (3). Protonation of β-amino conjugated enones on carbonyl oxygen gives a β-imino enol system (4). Ricca and co-workers reported (5) that upon heating of this protonated compounds, aminoacetophenones and pyridines were obtained. They proposed the formation of 3-acetyl-4-methyl-4-amino-6-oxo-2-heptyl cation as an intermediate in their reaction from 4-amino-3-penten-2-one to 4,6-dimethyl-2-aminoacetophenone and 2,4,6-trimethyl-3-acetylpyridine. When β-amino conjugated enones are treated with trimethylchlorosilane (TMSC), a similar cyclization reaction is expected by the strong affinity between oxygen and silicon.

The reaction of 4-amino-3-penten-2-one (Ia) with TMSC at room temperature did not give any expected product and the starting substances were recovered. Though we did not succeed in isolation of trimethylsilyl β-imino enol ether (IV), the expected amino acetophenones (II) and/or pyridines (III) were obtained under the similar reaction conditions at 125°. The reaction of 4-(*N*-ethyl)amino-3-penten-2-one (Ic) gave 4,6-dimethyl-2-(*N*-ethyl)aminoacetophenone (IIc) and 2,4,6-trimethyl-3-acetylpyridine (IIIa), which were identical with the products obtained from the reaction of Ic according to Ricca's conditions. Similar treatment of Ia with TMSC afforded IIIa, while that of 4-(1-pyrrolidinyl)-3-penten-2-one (Ih) afforded 4,6-dimethyl-2-(1-pyrrolydinyl)acetophenone (IIh). The results listed in Table I indicated that half molar amount of TMSC was necessary to form II and III. Further, *N*-substituted or *N,N*-disubstituted 4-amino-3-penten-2-ones (I) were treated with half molar amount of TMSC. The results in Table 2 show that the yield of II increases in the case of I with bulky substituents on nitrogen.



a: R= Me, R^1=R^2= H
b: R=R^1= Me, R^2= H
c: R= Me, R^1= Et, R^2= H
d: R= Me, R^1= Pr, R^2= H
e: R= Me, R^1= i-Pr, R^2= H
f: R= Me, R^1= Bu, R^2= H
g: R=R^1=R^2= Me
h: R= Me, R^1, R^2= $(CH_2)_4$
i: R= Me, R^1, R^2= $(CH_2)_5$
j: R= Me, R^1, R^2= $(CH_2)_2O(CH_2)_2$
k: R= Et, R^1=R^2= H
l: R= Pr, R^1=R^2= H
m: R= Pr, R^1= Bu, R^2= H
n: R= Pr, R^1, R^2= $(CH_2)_4$

Scheme 1

Table 1

Reaction of Ia and Ih with TMSC at 125°

Compound No.	R^1	R^2	Amount of TMSC (Mole)	Isolated Yield (%) II	III
Ia	H	H	0.26	0	54
			0.49	0	92
			1.00	0	97
			1.99	0	98
Ih	$(CH_2)_4$		0.25	50	0
			0.51	87	0
			1.00	82	0
			1.99	32	0

When 5-amino-4-hexen-3-one (Ik) and 2-amino-3-hepten-4-one (Il) were treated with TMSC, 3-propanoyl-2,4-dimethyl-6-ethylpyridine (IIIk) and 3-butanoyl-2,4-dimethyl-6-propylpyridine (IIIl) were respectively obtained. The structures of these products were deduced from the ir, nmr and elemental analysis data. Further, the structure of 3-(1-hydroxypropyl)-2,4-dimethyl-6-ethylpyridine (V), which was derived from IIIk by sodium borohydride reduction, was confirmed by the nmr spectrum in the presence of europium shift reagent. Similarly, the reaction products from 2-(*N*-butyl)amino- (Im) and 2-(1-pyrrolidinyl)-3-hepten-4-one (In) were found to be 2-(*N*-butyl)amino- (IIm) and 2-(1-pyrrolidinyl)-4-methyl-6-propylbutyrophenone (IIn), respectively.

From these results, we assumed the following reaction mechanism showing in Scheme 2. β-Amino conjugated enone (I) reacts with TMSC to form trimethylsilyl β-imino enol ether (IV). This intermediate IV is attacked by

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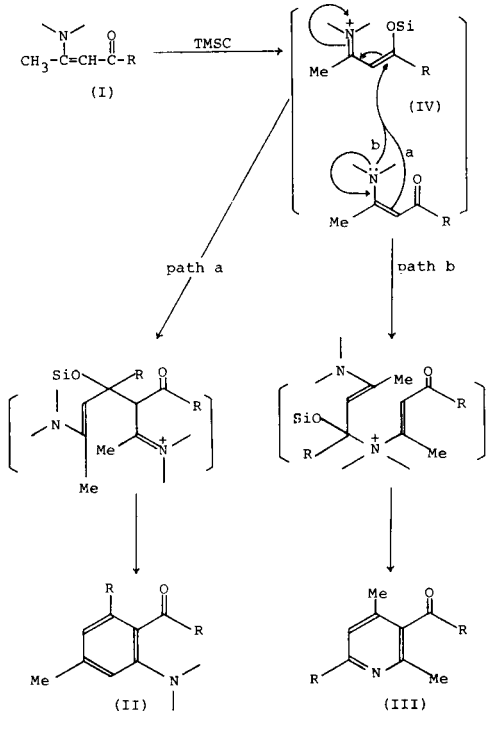
Table 2

Reaction of 4-Amino-3-penten-2-ones (I) with TMSC

Compound No.	R^1	R^2	Temperature (°C)	Time (hours)	Isolated Yield (%) II	III
Ia	H	H	125	4.5	0	92
Ib	Me	H	145	36	20	40
Ic	Et	H	125	36	28	8
Id	Pr	H	125	36	46	1
Ie	*i*-Pr	H	125	36	69	0
If	Bu	H	125	36	53	1
Ig	Me	Me	125	24	95	0
Ih	$(CH_2)_4$		125	24	87	0
Ii	$(CH_2)_5$		125	24	96	0
Ij	$(CH_2)_2O(CH_2)_2$		125	24	63	0



Scheme 2

β-amino conjugated enone (I) and then cyclizes. When amino nitrogen of I as a nucleophile attacks IV, path b, pyridine derivative III is formed. On the contrary, the attack of α-carbon of I to IV gives amino acetophenone derivative II.

EXPERIMENTAL

Melting points were uncorrected. Uv spectra were recorded on a Jasco UVIDEC-1 ultraviolet and visible absorption spectrometer. Infrared (ir) spectra were obtained on a Hitachi 215 type infrared absorption spectrometer. Nuclear magnetic resonance (nmr) spectra were measured on a Hitachi H-60 type nmr spectrometer using tetramethylsilane as an internal standard. Mass spectra were measured on Hitachi 6MG-GC mass spectrometer.

General Procedure of the Reaction of I with TMSC.

To a solution of β-amino conjugated enones (10 mmoles) in dry benzene (20 ml.) was added trimethylchlorosilane (TMSC) (6 mmoles), and this mixture was heated at 125° in a sealed tube for 24 hours. The mixture was then concentrated, the residue was dissolved in dichloromethane and washed with sodium hydrogencarbonate solution. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated off to give a crude product. This crude product was purified by silica gel column chromatography with benzene as a eluent and/or by fractional distillation. Compounds IIc, IIg, IIh and IIIa were identified with authentic samples by spectral data and chromatographic behaviors.

2-(*N*-Methyl)amino-4,6-dimethylacetophenone (IIb).

This compound had b.p. 95-100°/5 mm; nmr (deuteriochloroform): δ 2.26 (s, 3H), 2.38 (s, 3H), 2.49 (s, 3H), 2.80 (broad s, 3H), 6.30 (s, 2H) and 6.35 ppm (broad s, 1H).

Anal. Calcd. for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.39; H, 8.47; N, 7.89.

2-(*N*-Propyl)amino-4,6-dimethylacetophenone (IId).

This compound had b.p. 123-130°/7 mm; nmr (deuteriochloroform): δ 0.98 (t, 3H, J = 6.2 Hz), 1.63 (m, 2H), 2.07 (s, 3H), 2.38 (s, 3H), 2.48 (s, 3H), 3.04 (t, 2H, J = 7.0 Hz), 5.9 (broad s, 1H) and 6.3 ppm (broad s, 2H); ms: m/e 205 (M^+), 190, 176, 158, 134 and 55.

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.05; H, 9.32; N, 6.82. Found: C, 76.07; H, 9.39; N, 6.57.

2-(*N*-Isopropyl)amino-4,6-dimethylacetophenone (IIe).

This compound had b.p. 130-135°/5 mm; nmr (deuteriochloroform): δ 1.19 (d, 6H, J = 6.1 Hz), 2.23 (s, 3H), 2.34 (s, 3H), 2.46 (s, 3H), 3.58 (sept, 1H), 6.25 (s, 1H), 6.33 (s, 1H) and 6.2-6.4 ppm (broad s, 1H).

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.05; H, 9.32; N, 6.82. Found: C, 76.39; H, 9.42; N, 7.05.

2-(*N*-Butyl)amino-4,6-dimethylacetophenone (IIf).

This compound had b.p. 130-132°/6 mm; nmr (deuteriochloroform): δ 0.93 (t, 3H), 1.52 (m, 4H), 2.23 (s, 3H), 2.35 (s, 3H), 2.45 (s, 3H), 3.01 (m, 2H), 6.32 (s, 1H), 6.34 (s, 1H) and 6.62 ppm (broad s, 1H); ir (neat): 3375, 2950, 2920, 2860, 1640, 1605, 840, 820 and 730 cm^{-1}; uv (ethanol): λ max 375 nm (log ε 4.49).

Anal. Calcd. for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.39. Found: C, 76.66; H, 9.55; N, 6.37.

2-(1-Piperidino)-4,6-dimethylacetophenone (IIi).

This compound had m.p. 68-69°; nmr (deuteriochloroform): δ 1.56 (m, 6H), 2.16 (s, 3H), 2.26 (s, 3H), 2.49 (s, 3H), 2.85 (m, 4H) and 6.73 ppm (broad s, 2H); ir (potassium bromide): 2920, 2840, 2785, 1680, 1600, 1570 and 845 cm^{-1}.

Anal. Calcd. for $C_{15}H_{21}NO$: C, 77.85; H, 9.15; N, 6.05. Found: C, 77,85; H, 9.13; N, 5.87.

2-(1-Morpholino)-4,6-dimethylacetophenone (IIj).

This compound had m.p. 75-75.5°; nmr (deuteriochloroform): δ 2.17 (s, 3H), 2.29 (s, 3H), 2.50 (s, 3H), 2.89 (m, 4H), 3.74 (m, 4H) and 6.74 ppm (s, 2H); ir (potassium bromide): 2940, 2900, 2830, 1680, 1595, 855 and 840 cm^{-1}.

Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.06; H, 8.16; N, 6.01.

3-Propanoyl-2,4-dimethyl-6-ethylpyridine (IIIk).

This compound had b.p. 218-220°, 98% yield; nmr (deuteriochloroform): δ 1.21 (t, 3H, J = 7.6 Hz), 1.28 (t, 3H, J = 7.6 Hz), 2.20 (s, 3H), 2.43 (s, 3H), 2.77 (q, 4H, J = 7.6 Hz) and 6.87 ppm (s, 1H); ir (neat): 2965, 2925, 2870, 1700, 1590, 950 and 865 cm^{-1}.

Anal. Calcd. for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 74.84; H, 8.77; N, 7.16.

3-Butanoyl-2,4-dimethyl-6-propylpyridine (IIIl).

This compound was obtained in 89% yield; nmr (deuteriochloroform): δ 0.97 (t, 6H), 1.73 (m, 4H), 2.16 (s, 3H), 2.40 (s, 3H), 2.68 (t, 4H) and 6.79 ppm (s, 1H); ir (neat): 2950, 2920, 2860, 1695, 1585 and 750 cm^{-1}.

Anal. Calcd. for $C_{14}H_{21}NO$: C, 76.66; H, 9.65; N, 6.39. Found: C, 76.66; H, 9.57; N, 6.26.

2-(*N*-Butyl)amino-4-methyl-6-propylbutryophenone IIm).

This compound was obtained in 45% yield; nmr (deuteriochloroform): δ 0.93 (t, 6H), 1.23-1.93 (m, 8H), 2.23 (s, 3H), 2.37-2.8 (m, 4H), 3.03 (m, 2H), 4.50 (broad s, 2H) and 6.30 ppm (s, 2H).

Anal. Calcd. for $C_{18}H_{29}NO$: C, 78.49; H, 10.61; N, 5.09. Found: C, 78.97; H, 10.42; N, 5.35.

2-(1-Pyrrolidinyl)-4-methyl-6-propylbutyrophenone (IIn).

This compound was obtained in 85% yield; nmr (deuteriochloroform): δ 0.93 (t, 3H, J = 7.0 Hz), 1.35-1.8 (m, 4H), 1.82 (m, 4H), 2.28 (s, 3H), 2.36 (m, 2H), 2.72 (t, 2H), 3.08 (m, 4H) and 6.53 ppm (broad s, 2H); ir (neat): 2940, 2900, 2850, 1680, 1595, 1560, 990 and 820 cm^{-1}.

Anal. Calcd. for $C_{18}H_{27}NO$: C, 79.07; H, 9.95; N, 5.12. Found: C, 78.97; H, 9.76; N, 5.29.

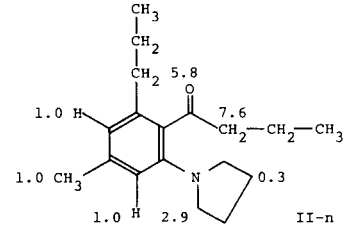
3-(1-Hydroxypropyl)-2,4-dimethyl-6-ethylpyridine (V).

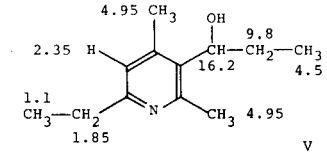
The compound IIIk (250 mg.) was reduced with excess sodium borohydride in ethanol. The product was purified by silica gel chromatography, m.p. 61.5-62.5°, 85% yield; nmr (deuteriochloroform): δ 0.93 (t, 3H, J = 7.2 Hz), 1.18 (t, 3H, J = 7.6 Hz), 1.85 (m, 2H), 2.40 (s, 3H), 2.63 (q, 2H, J = 7.6 Hz), 4.2 (broad s, 1H), 4.96 (t, 1H, J = 6.4 Hz) and 6.75 ppm (s, 1H); ir (potassium bromide): 3200, 2955, 2920, 2860, 1595, 1555, 1100 and 735 cm^{-1}.

Anal. Calcd. for $C_{12}H_{19}NO$: C, 74.56; H, 9.90; N, 7.24. Found: C, 74.73; H, 10.06; N, 7.24.

Eu Induced Shift Analysis of IIn and V.

Nmr spectra of deuteriochloroform solutions of IIn and V were measured in the presence of $Eu(dpm)_3$, and the molar induced shift values are summarized in Scheme 3.





The Molar Induced Shift Values of II-n and V

Scheme 3

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