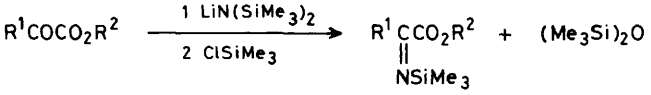
Preparation of α-(*N*-Trimethylsilyl)imino Esters and Their Use in the Synthesis of α-Amino Esters and 2-Alkoxycarbonylimidazol-4(2*H*)-ones

Yoshihiko Matsuda, Shigeo Tanimoto,* Tadashi Okamoto, and Syed Mashhood Ali
Institute for Chemical Research, Kyoto University, Uji, Kyoto 611, Japan

The reaction of α-keto esters with lithium 1,1,1,3,3,3-hexamethyldisilazanide afforded α-(*N*-trimethylsilyl)imino esters in good yields, which were reduced to the corresponding α-amino esters by reducing agents such as $NaBH_3CN$. α-(*N*-Trimethylsilyl)imino esters were treated with methanol to afford 2-alkoxycarbonylimidazole-4(2*H*)-ones *via* dimerization of the intermediate α-imino esters.

The carboxylic esters with an imino or *N*-substituted imino group in the α-position seem to be potentially useful intermediates for α-amino ester synthesis.[1,2] They have already been used for this purpose, although they have proved expensive and/or difficult to prepare. For many years, we have focused our attention on this field and, for example,

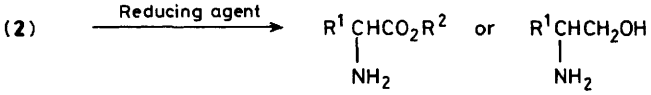


(1) (2)

	R^1	R^2
a;	Ph	Me
b;	Ph	Et
c;	Bu^t	Me
d;	Bu^t	Et
e;	Ph	Bu^t

synthesized methyl 1-phenyl-(*N*-tosylimino)acetate and used it in the synthesis of the corresponding α-*N*-tosylamino ester.[3] Our continued investigation of the carboxylic esters having *N*-substituted imino groups has shown that α-keto esters, when treated with lithium 1,1,1,3,3,3-hexamethyldisilazanide in tetrahydrofuran (THF), afford the title compounds, α-(*N*-trimethylsilyl)imino esters (**2**) in good yields (Table 1). As in the reaction of ketones with sodium hexamethyldisilazanide,[4] the present reaction seems to proceed *via* initial formation of the lithium hexamethyldisilazanide-addition product of (**1**) and subsequent elimination of lithium trimethylsilanolate. The liberated lithium salt is trapped by the lastly added chlorotrimethylsilane to give hexamethyldisiloxane.

Compounds (**2a**) and (**2c**) can be reduced to the corresponding α-amino esters [(**3a**) and (**3c**)] or β-amino alcohols [(**4a**) and (**4c**)] with a variety of reducing agents listed



	R^1	R^2	(3)	(4)
a;	Ph	Me		
c;	Bu^t	Me		

† The α-imino ester is unstable and easily dimerizes with elimination of methanol. However, the reduction of α-imino ester in the reaction system seems to occur more rapidly than the dimerization.

Table 1. Reaction of α-keto esters (**1**) with lithium 1,1,1,3,3,3-hexamethyldisilazanide in THF

Run	Substrate	Product	Yield (%)[a]
1	(**1a**)	(**2a**)	77
2	(**1b**)	(**2b**)	75
3	(**1c**)	(**2c**)	80
4	(**1d**)	(**2d**)	64
5	(**1e**)	(**2e**)	85

[a] Yield of isolated products by distillation.

Table 2. Reduction of α-(*N*-trimethylsilyl)imino esters (**2**) with a variety of reducing agents

Run	Substrate	Reducing agent	Solvent	Product	Yield (%)[a]
1	(**2a**)	$NaBH_3CN$	MeOH	(**3a**)	40
2	(**2a**)	$NaBH_4$	MeOH	(**3a**)	44
3	(**2a**)	$Me_2NH{\cdot}BH_3$	MeOH	(**3a**)	43
4	(**2a**)	$LiAlH_4$	THF	(**4a**)	95[b]
5	(**2c**)	$NaBH_3CN$	MeOH	(**3c**)	90
6	(**2c**)	$NaBH_4$	MeOH	(**3c**)	38
7	(**2c**)	$Me_2NH{\cdot}BH_3$	MeOH	(**3c**)	38
8	(**2c**)	Bu_3SnH	MeOH	(**3c**)	84
9	(**2c**)	$LiAlH_4$	THF	(**4c**)	85[b]

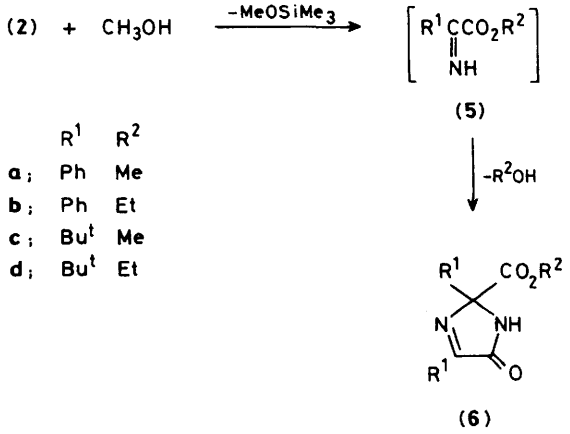
[a] Determined by g.l.c. analysis using decane as an internal standard. [b] Only in these cases do the yields refer to those obtained by distillation under reduced pressure.

in Table 2. These reductions, except with $LiAlH_4$, were carried out under the same reaction conditions. The methods of reduction seem to be generally practicable for preparation of α-amino esters from various α-(*N*-trimethylsilyl)imino esters other than (**2a**) and (**2c**). When aprotic THF or dichloromethane was used instead of protic methanol as the reaction medium, the starting (**2a**) or (**2c**) was recovered unchanged, suggesting that the reduction in methanol occurred only *via* the intermediate α-imino esters derived from (**2a**) or (**2c**) and methanol.† Probably, the bulkiness of the trimethylsilyl group of (**2a**) or (**2c**) prevents the reduction in THF or dichloromethane from occurring by attack of these reducing agents. In the cases with $LiAlH_4$, both the (*N*-trimethylsilyl)imino and methoxycarbonyl groups of (**2a**) and (**2c**) have been reduced without any resistance to give (**4a**) and (**4c**), respectively, in high yields (95 and 85%).

The C=N bond of (**2a**) could also be catalytically hydrogenated under an atmosphere of hydrogen in the presence of a catalyst composed of bis(dimethylglyoximato)cobalt [$Co(Hdmg)_2{\cdot}2H_2O$] (0.1 mol equiv.) and pyridine (0.12 mol

equiv.) per mole of (**2a**). Compound (**3a**) was obtained in 87% yield, although, an increase in the amount of $Co(Hdmg)_2 \cdot 2H_2O$ and pyridine lowered this. These results prompted us to investigate the asymmetric hydrogenation of (**2a**) under an atmosphere of hydrogen in the presence of $Co(Hdmg)_2 \cdot 2H_2O$ (0.1 mol equiv.) and a chiral reagent (0.12 mol equiv.) per mole of (**2a**). The asymmetric hydrogenation was attempted using many commercially available chiral reagents, however, only the attempts with $[Co(Hdmg)_2 \cdot 2H_2O]$-L-proline methyl ester and $[Co(Hdmg)_2 \cdot 2H_2O]$-L-proline hydrochloride were successful [e.e. was 2.33* (chemical yield, 90%) and 1.03%* (chemical yield, 52%), respectively]. In all other cases, desilylation of (**2a**) followed by dimerization of the intermediate α-imino ester (**5a**) accompanied by the release of methanol was preferred. This was ascertained by isolating the dimer (**6a**) from the reaction mixture.

In the course of studies described above, we noticed that α-(*N*-trimethylsilyl)imino esters such as (**2a**) are transformed into



another compound on contact with methanol. Thus, compounds (**2**) except (**2e**) were treated with methanol at room temperature (20 °C) or 50—60 °C. After removal of volatile components, the solid residue was purified to give 2-alkoxycarbonylimidazole-4(2*H*)-ones (**6**) (Table 3). The reaction seems to proceed *via* a process involving condensation of (**2**) with methanol and subsequent dimerization of intermediate α-imino ester (**5**) with elimination of one molecule of alcohol. In the reaction with (**2c**) or (**2d**) as the substrate at room temperature, the crude intermediate (**5c**) or (**5d**) was isolated by the careful removal of volatile components from the reaction mixture. The structures of these intermediates were confirmed spectroscopically without further purification. Also, these intermediates when heated were easily converted into the corresponding dimers (**6c**) and (**6d**), respectively, with the evolution of methanol and ethanol. When (**2a**) or (**2b**) was used the isolation of intermediate (**5a**) or (**5b**) was impossible due to its rapid dimerization at room temperature. The structures of products (**6**) were elucidated from their ^1H n.m.r., ^{13}C n.m.r., i.r. spectra, as well as microanalyses (Table 5). Also, the fragmentation patterns of mass spectra were in good accord with the assigned structures.

In order to establish the character of the imidazole-4(2*H*)-one ring, we examined the reaction of (**6a**) with several alkyl halides in the presence of KOH. When (**6a**) was treated with a slight excess of alkyl halide and KOH, (**7a**) or (**8a**) was obtained selectively depending upon the alkyl halide used. The compounds (**7a**; R^3 = Me), (**7a**; R^3 = Et), and (**7a**; R^3 = $PhCH_2$) were normal *N*(3)-alkylated products. However, the

* These values refer to the following report: L. Arpesella, A. L. Manna, and M. Grassi, *Gazz. Chim. Ital.*, 1955, **85**, 1354.

Table 3. Reaction of α-(*N*-trimethylsilyl)imino esters (**2**) with methanol

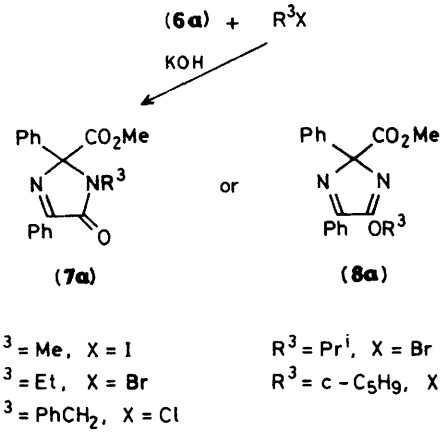
Run	Substrate	Reaction temp. (°C)[a]	Product	Yield (%)[b]
1	(**2a**)	20	(**6a**)	87
2	(**2b**)	20	(**6b**)	76
3	(**2c**)	50—60	(**6c**)	50
4	(**2d**)	50—60	(**6d**)	50

[a] In all runs the reaction period was 1 h. [b] Isolated yields by column chromatography.

Table 4. Reaction of (**6a**) with some alkyl halides in the presence of KOH

Run	Substrate	Alkyl halide	Product	Yield (%)[a]
1	(**6a**)	MeI	(**7a**; R^3 = Me)	88
2	(**6a**)	EtBr	(**7a**; R^3 = Et)	67
3	(**6a**)	$PhCH_2Cl$	(**7a**; R^3 = $PhCH_2$)	63
4	(**6a**)	Pr^iBr	(**8a**; R^3 = Pr^i)	80
5	(**6a**)	c-C_5H_9Br	(**8a**; R^3 = c-C_5H_9)	50

[a] Isolated yield by column chromatography.



products [(**8a**; R^3 = Pr^i) and (**8a**; R^3 = *c*-C_5H_9)] derived from the latter two α-branched alkyl halides seem to have structures similar to those derived from *O*-alkylation of the carbonyl group of the ring. This is because the protons at carbons participating in the bond formations appear approximately at δ 5.3—5.4 and 5.5—5.6, respectively, as a multiplet (Table 5). However, we have no further evidence.

Experimental

^1H and ^{13}C n.m.r. spectra were recorded on a Varian VXR-200 spectrometer in $CDCl_3$. The i.r. spectra were recorded on a JASCO IR-810 spectrophotometer. The microanalyses were performed using a Yanaco MT-3. The mass spectral data were obtained on a JEOL JMS-DX-300 spectrometer.

Preparation of α-(N-*Trimethylsilyl*)*imino Esters* (**2**).—Under an argon atmosphere 1,1,1,3,3,3-hexamethyldisilazane (17.9 g, 0.11 mol) was mixed with butyl-lithium (1.56M, 70.5 ml, 0.11 mol) in hexane with stirring at 0 °C, and the resulting mixture was further stirred for 0.5 h at that temperature. To the cooled (−78 °C) mixture was added slowly over a period of 1 h an α-keto ester (**1**) (0.10 mol) in dry THF (35 ml). After the addition, the mixture was warmed to 0 °C and stirred for 1 h, and then chlorotrimethylsilane (13.0 g, 0.12 mol) was added with cooling. The mixture was then stirred continuously at room temperature until precipitation of a white solid was

Table 5. Physical and spectral data of the products obtained (except the known compounds)

Product	M.p. (°C)[a] or [b.p. (°C/mmHg)]	^{1}H N.m.r. (δ in $CDCl_3$)[b]
(**2a**)	(85/1)	0.25 (s, 9 H), 3.86 (s, 3 H), 7.4—7.6 (m, 3 H), 7.7—7.9 (m, 2 H)
(**2b**)	(92—93/1)	0.24 (s, 9 H), 1.38 (t, 3 H), 4.35 (q, 2 H), 7.4—7.5 (m, 3 H), 7.7—7.8 (m, 2 H)
(**2c**)	(80—81/22)	0.10 (s, 9 H), 1.12 (s, 9 H), 3.72 (s, 3 H)
(**2d**)	(80/18)	0.08 (s, 9 H), 1.11 (s, 9 H), 1.29 (t, 3 H), 4.16 (q, 2 H)
(**2e**)	(105—110/1)	0.29 (s, 9 H), 1.61 (s, 9 H), 7.3—7.5 (m, 3 H), 7.7—7.8 (m, 2 H)
(**6a**)[c]	145	3.80 (s, 3 H), 7.4—7.7 (m, 8 H), 8.5—8.6 (m, 2 H), 9.37 (s, 1 H)
(**6b**)[c]	148	1.26 (t, 3 H), 4.26 and 4.27 (q and q, 2 H), 7.3—7.7 (m, 8 H), 8.4—8.5 (m, 2 H), 8.64 (s, 1 H)
(**6c**)[c]	95	0.99 (s, 9 H), 1.35 (s, 9 H), 3.78 (s, 3 H), 7.52 (s, 1 H)
(**6d**)[c]	100	1.00 (s, 9 H), 1.29 (t, 3 H), 1.34 (s, 9 H), 4.20 (q, 2 H), 7.72 (s, 1 H)
(**7a**; R^3 = Me)	92	3.04 (s, 3 H), 3.86 (s, 3 H), 7.2—7.6 (m, 8 H), 8.5—8.6 (m, 2 H)
(**7a**; R^3 = Et)	95	0.94 (t, 3 H), 3.57 and 3.59 (q and q, 2 H), 3.87 (s, 3 H), 7.2—7.6 (m, 8 H), 8.5—8.6 (m, 2 H)
(**7a**; R^3 = $PhCH_2$)	Not measured	3.54 (s, 3 H), 4.63 (d, 1 H), 4.94 (d, 1 H), 7.0—8.6 (m, 15 H)
(**8a**; R^3 = Pr^i)	98	1.48 (d, 3 H), 1.51 (d, 3 H), 3.71 (s, 3 H), 5.3—5.4 (m, 1 H), 7.3—7.6 (m, 6 H), 7.8—7.9 (m, 2 H), 8.2—8.3 (m, 2 H)
(**8a**; R^3 = c-C_5H_9)	115	1.6—2.1 (m, 8 H), 3.72 (s, 3 H), 5.5—5.6 (m, 1 H), 7.3—8.3 (m, 10 H)

[a] M.p.s are those obtained after repeated chromatographic purifications (without recrystallization with solvent). [b] Measured at 200 MHz. [c] ^{13}C N.m.r. [δ($CDCl_3$)] of these compounds are as follows: (**6a**) 53.82, 86.98, 126.35, 128.58, 128.82, 129.02, 129.27, 129.68, 132.38, 136.84, 163.19, 165.95, 168.57; (**6b**) 13.95, 63.14, 86.14, 126.21, 128.54, 128.80, 128.99, 129.23, 129.69, 132.32, 136.87; (**6c**) 24.99, 26.96, 35.80, 38.93, 52.68, 90.18, 165.00, 168.41, 175.72; (**6d**) 14.06, 25.03, 26.97, 35.06, 38.80, 61.94, 90.04, 156.06, 167.68, 175.50.

complete. After removal of the latter, (**2**) was isolated by distillation under reduced pressure.

Reduction of (**2a**) *and* (**2c**) *with a Variety of Reducing Agents except* $LiAlH_4$.—Compound (**2a**) (235 mg, 1.0 mmol) or (**2c**) (215 mg, 1.0 mmol) was added to a mixture of the reducing agent (1.0 mmol) in dry methanol (2 ml) at 0 °C under argon. The mixture was stirred for 15 min at room temperature and treated with water (10 ml). It was then extracted with ether (3 × 10 ml), and the combined extracts were dried ($MgSO_4$) and concentrated to afford a residue which was distilled under reduced pressure.

Reduction of (**2a**) *and* (**2c**) *with* $LiAlH_4$.—Compound (**2a**) (235 mg, 1.0 mmol) or (**2c**) (215 mg, 1.0 mmol) was added to a mixture of $LiAlH_4$ (152 mg, 4.0 mmol) in THF (4 ml) at 0 °C under argon. The mixture was refluxed under an argon atomosphere and treated with water (10 ml). It was then extracted with ether (3 × 10 ml), and the combined extracts were dried ($MgSO_4$) and distilled under reduced pressure.

Catalytic Hydrogenation of (**2a**) *by* $Co(Hdmg)_2 \cdot 2H_2O$–*Chiral Reagent* (*or Pyridine*) *Complex*.—The catalyst $Co(Hdmg)_2 \cdot 2H_2O$ (32.5 mg, 0.1 mmol) was mixed with dry methanol (1 ml) at room temperature under argon and then the chiral reagent (0.12 mmol) (or pyridine, 9.4 mg, 0.12 mmol) and (**2a**) (235 mg, 1.0 mmol) in THF (2 ml) were added successively. The system was filled with hydrogen by connecting it to a hydrogen-containing vessel. After being stirred for 10 h at room temperature, the system was treated with a large quantity of ether. The mixture was then filtered and the precipitate was washed with ether. The combined filtrate and washings were then dried ($MgSO_4$) and distilled under reduced pressure to afford a residue which was again distilled under reduced pressure.

Reaction of α-(N-*Trimethylsilyl*)*imino Esters* (**2**) *with Methanol*.—Either (**2a**), (**2b**), (**2c**), or (**2d**) (1.0 mmol) was mixed with dry methanol (2 ml) at 0 °C under argon. After the mixture had been stirred for 1 h at room temperature (20 °C) or at 50—60 °C, the volatile components were removed under reduced pressure to afford a residue. The residue was washed with a small amount of pentane and subjected to column chromatography (silica gel, 20% ethyl acetate–hexane as eluant).

Reaction of (**6a**) *with Several Alkyl Halides in the Presence of* KOH.—The alkyl halide (0.6 mmol) was added to a solution of (**6a**) (147 mg, 0.5 mmol) and KOH (34 mg, 0.6 mmol) in dry dimethyl sulphoxide (1 ml). The mixture was then stirred for 1 h at room temperature, and extracted with dichloromethane (3 × 10 ml). The dichloromethane extracts were combined and evaporated under reduced pressure to afford a residue which was subjected to column chromatography (silica gel, 20% ethyl acetate–hexane as eluant).

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