Reactions of Trimethylsilyl Ketene Acetals with Benzoyl Cyanide and with α-Keto Esters

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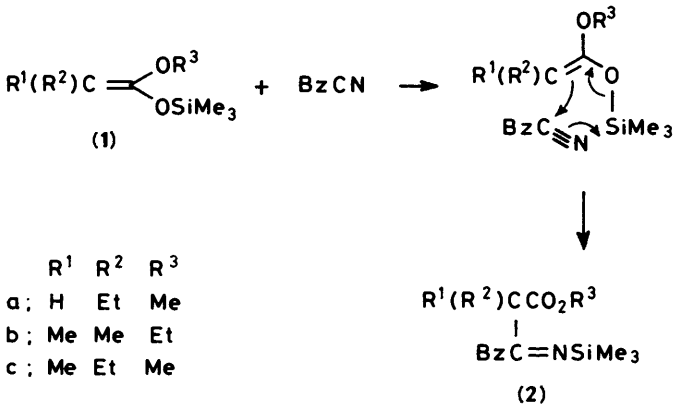
Trimethylsilyl ketene acetals reacted with benzoyl cyanide in the absence of a catalyst to give *N*-trimethylsilyl-β-benzoyl-β-iminopropionates. In the presence of a Lewis acid catalyst they gave the corresponding α-benzoylcarboxylates in moderate yields. Several new malates have been synthesized by condensing the acetals with α-keto esters in the presence of the same catalyst.

The reactions of silyl ketene acetals with carbon electrophiles under neutral or Lewis acid-catalysed conditions [1] give, in most cases, the corresponding α-substituted carboxylates *via* a process involving electrophilic attack by the carbon and simultaneous release of the trimethylsilyl group. Recently, we found [2] that several trimethylsilyl ketene acetals reacted smoothly with Vilsmeier reagents to give moderate yields of the corresponding α-formylcarboxylates, a result which suggests that, when treating trimethylsilyl ketene acetals with extremely electrophilic reagents, there is no need for a Lewis acid catalyst. With this in mind we have examined the reaction of trimethylsilyl ketene acetals with benzoyl cyanide or with methyl phenylglyoxylate (or ethyl pyruvate) in the absence of a catalyst, the electrophilicity of these carbonyl groups being heightened by the electron-withdrawing effect of the adjacent cyano or ester group.

Trimethylsilyl ketene acetals (**1**) and benzoyl cyanide reacted when stirred in dichloromethane at room temperature without any catalyst (Scheme 1 and Table 1). The reaction seems to



Scheme 1.

proceed *via* a process involving electrophilic attack of the cyano group of benzoyl cyanide and simultaneous migration of the trimethylsilyl group from the ester group of the substrate to the nitrogen of the cyano group. As the group which participated in the electrophilic attack was not the carbonyl but the cyano group of benzoyl cyanide, this suggests that the cyanide group alone, such as in benzyl cyanide, could undergo a similar reaction with trimethylsilyl ketene acetals. In each case, however, a side-reaction gave rise to the corresponding α-benzoylcarboxylates (**3**). In order to supress this side-reaction and increase the yields of the *N*-silylated β-benzoyl-β-iminopropionates (**2**), the use of rhodium complexes such as $[Rh_4(CO)_{12}]$† is now being investigated.

Table 1. Reaction of trimethylsilyl ketene acetals (**1**) with benzoyl cyanide in CH_2Cl_2 in the absence of a catalyst

Run	Substrate	Product[a]	Yield (%)[b]
1	(**1a**)	(**2a**)	30
2	(**1b**)	(**2b**)	28
3	(**1c**)	(**2c**)	27

[a] The formation of a significant amount of the corresponding α-benzoylcarboxylate was found in each run. [b] Yield of isolated products based on compound (**1**).

Reactions of the same substrates with benzoyl cyanide in the presence of a Lewis acid catalyst such as $TiCl_4$, $MeOH{\cdot}2TiCl_4$,‡ or Ti[(+)-DPT]Cl_2§ gave complete suppression of the above mentioned trans-silylation, with only the corresponding α-benzoylcarboxylate (**3**) being formed. This suggests that the reaction proceeds *via* a process involving electrophilic attack of the carbonyl group (not the cyano group) of benzoyl cyanide and simultaneous release of the trimethylsilyl group. The resulting β-cyano-β-hydroxy-β-phenylpropionates were converted into compound (**3**) with evolution of HCN (Scheme 2 and Table 2).

Silyl enol ethers react with acetyl cyanide [5] to give the corresponding β-cyano-β-hydroxy carbonyl compounds, no HCN being evolved. Under our reaction conditions, however, the initially formed β-cyano-β-hydroxy-β-phenylpropionate were unstable, probably owing to the electron-withdrawing effect and/or steric requirement of the phenyl group. Since it seems unlikely that a slight difference in the conditions induced a change in the course of the reaction, a convenient means of benzoylating carboxylates under acidic conditions has been found.¶ Further, a preliminary experiment suggests that Ti[(+)-DPT]Cl_2 may be used instead of $TiCl_4$ or $MeOH{\cdot}2TiCl_4$ as the catalyst. An attempt to synthesize an asymmetric α-benzoylcarboxylate using Ti[(+)-DPT]Cl_2 was impracticable, the stereochemistry of compound (**1**) being uncertain.

Next, we examined the reaction of some trimethylsilyl ketene acetals with ethyl pyruvate or methyl phenylglyoxylate in

† Recently, an aldol reaction of trimethylsilyl enol ether with aldehyde was aided by $[Rh_4(CO)_{12}]$ to afford the corresponding β-siloxy ketone.[3]

‡ The exact structure of this catalyst is uncertain, but it has been used in a cross-aldol-type reaction of alkenyl sulphide with trimethylsilyl enol ether.[4]

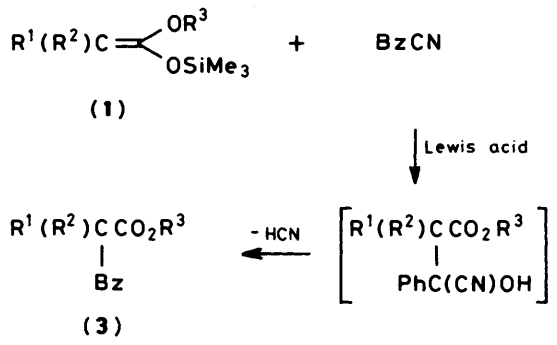
§ Ti[(+)-DPT]Cl_2 [DPT = $Pr^iCO_2C(O)HC(O)HCO_2Pr^i$] was prepared *in situ* by mixing $TiCl_4$ and di-isopropyl-(+)-tartrate in the presence of triethylamine.

¶ As far as the benzoylation of the hydroxy group, using benzoyl cyanide under basic conditions, is concerned several reports are given in the literature, for example, see ref. 6.

Table 2. Reaction of trimethylsilyl ketene acetals (1) with benzoyl cyanide in the presence of a Lewis acid catalyst

Run	Substrate	Catalyst (mol equiv. per substrate)	Procedure[a]	Product	Yield (%)[b]
1	(1a)	MeOH·2TiCl$_4$[c] (1:1)	B	(3a)	47
2	(1b)	TiCl$_4$ (0.5)	A	(3b)	51
3	(1b)	MeOH·2TiCl$_4$[c] (1:1)	B	(3b)	59
4	(1c)	TiCl$_4$ (0.5)	A	(3c)	44
5	(1d)	TiCl$_4$ (0.5)	A	(3d)	57
6	(1e)	MeOH·2TiCl$_4$[c] (1:1)	B	(3e)	46
7	(1f)	TiCl$_4$ (0.5)	A	(3f)	65
8	(1f)	MeOH·2TiCl$_4$[c] (1:1)	B	(3f)	51
9	(1g)	MeOH·2TiCl$_4$[c] (1:1)	B	(3g)	53
10	(1h)	TiCl$_4$ (0.5)	A	(3h)	47

[a] See Experimental section. [b] Yields of isolated products based on compound (1). [c] This catalyst has already been used by Takeda and his co-workers (see ref. 4).



	R^1	R^2	R^3
a	H	Et	Me
b	Me	Me	Et
c	Me	Et	Me
d	H	Et	Et
e	H	Pr	Me
f	H	Pr^i	Et
g	H	Pr^i	Me
h	Et	Et	Et

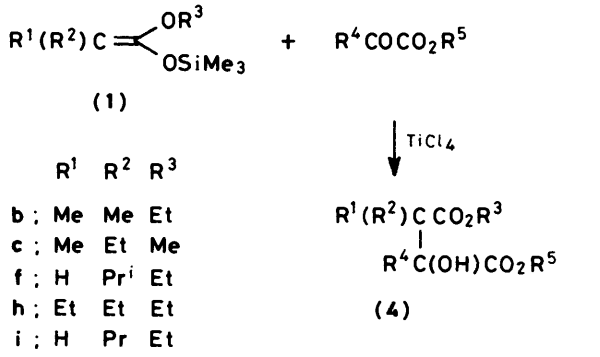
Scheme 2.

dichloromethane in the absence of catalyst: there was no reaction at room temperature, suggesting that such α-keto esters are less nucleophilic than benzoyl cyanide. As far as the Lewis acid-catalysed reaction of the same substrates with α-keto esters is concerned, Ojima and his co-workers[7] have reported that some silyl ketene acetals undergo electrophilic attack by (−)-menthyl pyruvate or phenylglyoxylate to give (−)-menthyl alkyl 2-methyl-or (−)-menthyl alkyl 2-phenyl-malate. There is, however, a lack of data concerning most of the 2-methyl (or phenyl)malates synthesized from trimethylsilyl ketene acetals and ethyl pyruvate or methyl phenylglyoxylate. Thus, we have treated several trimethylsilyl ketene acetals with the above-mentioned α-keto esters to obtain the novel 2-methyl (or phenyl) malates (4) (Scheme 3): the results are shown in Tables 3 and 4.

Table 3. Reaction of trimethylsilyl ketene acetals (1) with α-keto esters in the presence of TiCl$_4$

Run	Substrate	α-Keto ester R^4	α-Keto ester R^5	Product	R^4	R^5	Yield (%)[a]
1	(1b)	Me	Et	(4b)	Me	Et	96
2	(1c)	Me	Me	(4c)	Me	Me	78
3	(1c)	Ph	Me	(4c)	Ph	Me	92
4	(1f)	Me	Et	(4f)	Me	Et	71
5	(1f)	Ph	Me	(4f)	Ph	Me	95
6	(1h)	Me	Et	(4h)	Me	Et	78
7	(1h)	Ph	Me	(4h)	Ph	Me	93
8	(1i)	Me	Et	(4i)	Me	Et	79
9	(1i)	Ph	Me	(4i)	Ph	Me	85

[a] Yields of isolated products based on α-keto esters used.



Scheme 3.

Experimental

^{1}H N.m.r. spectra were determined on a Varian EM-360 spectrometer in $CDCl_3$ with $SiMe_4$ as an internal standard. The starting substrates (1) were prepared by the method of Ainsworth and his co-workers.[11] Dichloromethane was dried by distillation over P_2O_5. All other reagents and solvents were obtained commercially.

Reaction of Trimethylsilyl Ketene Acetals (1) *with Benzoyl Cyanide in the Absence of Catalyst* (*Table 1*).—A solution of either compound (**1a**), (**1b**), or (**1c**) (10 mmol) in dry dichloromethane (8 ml) was mixed with a solution of benzoyl cyanide (1.31 g, 10 mmol) in dry dichloromethane (5 ml). The resultant pale yellow reaction mixture was stirred overnight at room temperature and dichloromethane (15 ml) was added in one portion. The dichloromethane solution was washed successively with water (2 × 8 ml), aqueous Na_2CO_3 (2 × 10 ml), and brine (12 ml), dried ($MgSO_4$), and concentrated under reduced pressure to afford a residue which was purified by column chromatography (silica gel, 10% ethyl acetate–hexane as eluant) to give either compound (**2a**), (**2b**), or (**2c**).

Reaction of Trimethylsilyl Ketene Acetals (1) *with Benzoyl Cyanide in the Presence of Lewis Acid Catalyst* (*Table 2*).—*Procedure A.* A solution of compound (1) (10 mmol) in dry dichloromethane (8 ml) was mixed with benzoyl cyanide (1.44 g, 11 mmol) in dry dichloromethane (5 ml). A solution of $TiCl_4$ (0.55 ml, 5 mmol) in dry dichloromethane (3 ml) was added to the cooled (ice-cold water), stirred mixture. The mixture was allowed to warm to room temperature, stirred overnight at that temperature, and then diluted with water (10 ml). The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 × 8 ml). The combined organic layers were washed successively with aqueous $NaHCO_3$ (10 ml) and brine

Table 4. Physical and analytical data of the products obtained

Product	R^4	R^5	B.p. (°C/mmHg)[a] (lit., b.p.)[b]	^{1}H N.m.r. (δ in $CDCl_3$)	Found (%) (Required) C	H	N	M^+
(**2a**)			116—118/0.15	0.18 (s, 9 H), 0.95 (t, 3 H), 1.9—2.1 (m, 2 H), 2.80 (t, 1 H), 3.45 (s, 3 H), 7.45 (b s, 5 H)	62.95 (62.91)	7.6 (7.59)	4.5 (4.59)	305
(**2b**)			155—160/3	0.15 (s, 9 H), 1.20 (s, 3 H), 1.24 (t, 3 H), 1.25 (s, 3 H), 4.05 (q, 2 H), 7.2—7.5 (m, 5 H)	63.75 (63.91)	7.95 (7.84)	4.35 (4.38)	319
(**2c**)			122/0.1	0.20 (s, 9 H), 0.86 (t, 3 H), 1.20 (s, 3 H), 2.25 (q, 2 H), 3.65 (s, 3 H), 7.40 (s, 5 H)	63.9 (63.91)	7.9 (7.84)	4.4 (4.38)	319
(**3a**)			105/0.2 (146—147/11)[8]	0.98 (t, 3 H), 2.05 (m, 2 H), 3.65 (s, 3 H), 4.23 (t, 1 H), 7.3—8.2 (m, 5 H)	70.0 (69.88)	6.9 (6.84)		206
(**3b**)			155/0.2 (98—100/0.35)[9]	1.02 (t, 3 H), 1.82 (s, 6, H), 4.08 (q, 2 H), 7.2—7.9 (m, 5 H)	71.0 (70.88)	7.35 (7.32)		220
(**3c**)			145—148/7	0.82 (t, 3 H), 1.50 (s, 3 H), 2.06 (q, 2 H), 3.60 (s, 3 H), 7.2—7.9 (m, 5 H)	70.9 (70.88)	7.35 (7.32)		220
(**3d**)			145—150/8 (150—152/0.6)[9]	0.96 (t, 3 H), 1.15 (t, 3 H), 2.05 (m, 2 H), 4.10 (t, 1 H), 4.15 (q, 2 H), 7.2—8.1 (m, 5 H)	70.85 (70.88)	7.35 (7.32)		220
(**3f**)			160—163/7 (108—110/0.5)[9]	1.00 (t, 3 H), 1.09 (d, 6 H), 2.3—3.1 (m, 1 H), 4.12 (d, 1 H), 4.15 (q, 2 H), 7.3—8.3 (m, 5 H)	71.8 (71.77)	7.75 (7.74)		234
(**3g**)			120/0.2	0.95 (d, 3 H), 1.04 (d, 3 H), 2.4—3.1 (m, 1 H), 3.70 (s, 3 H), 4.09 (d, 1 H), 7.3—8.3 (m, 5 H)	70.8 (70.88)	7.4 (7.32)		220
(**3h**)			150—155/7 (173—175/15)[10]	0.76 (t, 6 H), 1.06 (t, 3 H), 2.10 (q, 4 H), 4.10 (q, 2 H), 7.2—8.0 (m, 5 H)	72.7 (72.55)	8.05 (8.12)		248
(**4b**)	Me	Et	90—95/6	1.23 (t, 3 H), 1.25 (t, 3 H), 1.28 (b s, 6 H), 1.41 (s, 3 H), 3.95 (s, 1 H), 4.15 (q, 2 H), 4.18 (q, 2 H)	57.0 (56.88)	8.7 (8.68)		232
(**4c**)	Me	Me	105—110/6	0.82 (t, 3 H), 1.16 (b s, 3 H), 1.28 (t, 3 H), 1.42 (b s, 3 H), 1.7—2.6 (m, 2 H), 3.66 (b s, 3 H), 4.07 and 4.10 (q and q, 2 H), 4.13 (s, 1 H)	56.8 (56.88)	8.8 (8.68)		232
(**4c**)	Ph	Me	155/7	0.73 (t, 3 H), 1.03 and 1.22 (s and s, 3 H), 1.9—2.6 (m, 2 H), 3.60 and 3.66 (s and s, 3 H), 3.80 (s, 3 H), 4.16 (s, 1 H), 7.1—7.7 (m, 5 H)	64.3 (64.27)	7.2 (7.19)		280
(**4f**)	Me	Et	115—120/6	0.93 (d, 6 H), 1.25 (t, 6 H), 1.35 (s, 3 H), 1.8—2.3 (m, 1 H), 2.68 (d, 1 H), 3.55 (s, 1 H), 4.15 (q, 4 H)	78.15 (78.02)	9.05 (9.00)		246
(**4f**)	Ph	Me	175—180/6—7	0.95 (d, 6 H), 1.20 (t, 3 H), 1.9—2.5 (m, 1 H), 3.41 (d, 1 H), 3.64 (s, 3 H), 3.75 (q, 2 H), 4.17 (s, 1 H), 7.0—7.7 (m, 5 H)	65.4 (65.29)	7.5 (7.53)		294
(**4h**)	Me	Et	135—140/7	0.88 (t, 6 H), 1.28 (t, 6 H), 1.40 and 1.46 (s and s, 3 H), 1.72 and 1.73 (q and q, 2 H), 3.92 (s, 1 H), 4.01 and 4.03 (q and q, 2 H)	60.0 (59.98)	9.25 (9.29)		260
(**4h**)	Ph	Me	180—185/6—7	0.54 (t, 3 H), 0.65 (t, 3 H), 1.22 (t, 3 H), 1.5—2.5 (m, 4 H), 3.75 b s, 3 H), 4.10 (q, 2 H), 4.53 (s, 1 H), 7.0—7.8 (m, 5 H)	66.35 (66.21)	7.9 (7.84)		308
(**4i**)	Me	Et	125—130/6	0.98 (t, 3 H), 1.27 (t, 3 H), 1.30 (t, 3 H), 1.42 (s, 3 H), 1.4—2.0 (m, 2 H), 2.5—2.9 (m, 2 H), 3.58 (d, 1 H), 4.10 (s, 1 H), 4.10 (q, 2 H), 4.15 (q, 2 H)	78.2 (78.02)	8.9 (9.00)		246
(**4i**)	Ph	Me	170—175/7	0.88 (t, 3 H), 1.00 (t, 3 H), 1.2—1.7 (m, 2 H), 1.7—2.3 (m, 2 H), 3.40 (d, 1 H), 3.72 (b s, 3 H), 3.86 (q, 2 H), 4.26 (s, 1 H), 7.0—7.7 (m, 5 H)	65.3 (65.29)	7.55 (7.53)		294

[a] Determined by bulb-to-bulb distillation. [b] The literature value, if it is provided, probably determined by ordinary distillation.

(10 ml), dried ($MgSO_4$), and concentrated under reduced pressure to afford a residue which was subjected to column chromatography (silica gel, 5% ethyl acetate–hexane as eluant) to give compound (**3**).

Procedure B. Methanol (0.22 ml, 5.5 mmol) in dry dichloromethane (5 ml) was added slowly at room temperature to a mixture of $TiCl_4$ (1.2 ml, 11 mmol) and dry dichloromethane (5.5 ml) and then the resulting pale yellow mixture was stirred for 1 h at that temperature. Benzoyl cyanide (0.66 g, 5 mmol) in dry dichloromethane (10 ml) at −78 °C under nitrogen was added slowly to the catalyst solution thus obtained and the resulting dark yellow mixture was stirred for 1 h at that temperature. After addition of a solution of compound (**1**) (5 mmol) in dry dichloromethane (5 ml) at −78 °C, the mixture was allowed to warm to room temperature and stirred overnight at that temperature under nitrogen. The resulting light brown mixture was then diluted with water (15 ml) and the organic layer was separated, and the aqueous layer was extracted with dichloromethane (2 × 8 ml). The combined organic layers were treated as above.

Reaction of Trimethylsilyl Ketene Acetals (**1**) *with α-Keto Esters in the Presence of* $TiCl_4$.—The α-keto ester (35 mmol) was added to a solution of compound (**1**) (53 mmol) in dry

dichloromethane (10 ml) at −15 °C under nitrogen, after which a solution of $TiCl_4$ (1.9 ml, 17.5 mmol) in dry dichloromethane (3 ml) was then added. The reaction mixture was allowed to warm to room temperature and stirred overnight at that temperature, and then treated with dry dichloromethane (15 ml). It was washed successively with aqueous $NaHCO_3$ (2 × 10 ml) and brine (10 ml), dried ($MgSO_4$), and concentrated under reduced pressure to afford a residue which was purified by column chromatography (silica gel, 20% ether–hexane as eluant) to give compound (**4**).

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