

## Novel $\alpha$ -Formylation of $\alpha,\alpha$ -Disubstituted Esters. Trimethylsilyl Trifluoromethanesulphonate-catalysed Reaction of Ketene Silyl Acetals with *N*-*t*-Butylformimidoyl Cyanide

Kohji Okano, Toshiaki Morimoto,\* and Minoru Sekiya

Shizuoka College of Pharmacy, Oshika, Shizuoka 422, Japan

General  $\alpha$ -formylation of  $\alpha,\alpha$ -disubstituted methyl acetates can be achieved by the reaction of ketene silyl acetals (**1**) with *N*-*t*-butylformimidoyl cyanide (**2**) in the presence of trimethylsilyl trifluoromethanesulphonate (**3**) as catalyst followed by hydrolysis of the products (**4**) and/or (**5**) with copper(II) acetate or hydrogen chloride in aqueous methanol.

The Claisen condensation under basic conditions constitutes an important method for the  $\alpha$ -formylation of esters using alkyl formate as a reagent.<sup>1</sup> Unfortunately, formylation of  $\alpha,\alpha$ -disubstituted esters results in low yields of the products,<sup>2</sup> because the reaction equilibrium is unfavourable for compounds lacking an acidic  $\alpha$ -hydrogen atom. Ketene silyl acetals (**1**) have been widely utilized as nucleophilic synthons for esters<sup>3</sup> and the reactions occur under mild and non-basic conditions. However, there appears to be only one example in which  $\alpha$ -formylated esters were obtained as by-products of the

reaction of (**1**) with dichloromethyl methyl ether in the presence of zinc chloride.<sup>4</sup>

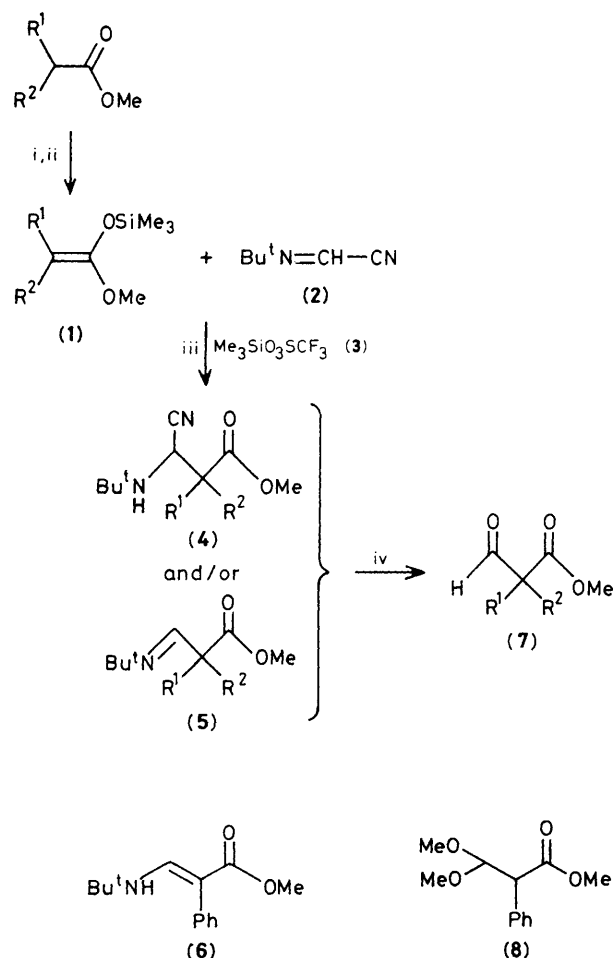
We now describe a new utilization of *N*-*t*-butylformimidoyl cyanide (**2**)<sup>†</sup> as an electrophilic reagent, which allows the  $\alpha$ -formylation of  $\alpha,\alpha$ -disubstituted esters to be carried out *via*

<sup>†</sup> The reagent (**2**) was prepared in good yield by a modification of the reported *N*-chlorination using *N*-chlorosuccinimide in place of calcium hypochlorite (see ref. 6).

**Table 1.** Trimethylsilyl trifluoromethanesulphonate (3)-catalysed reaction<sup>a</sup> of ketene silyl acetals (1) with *N*-*t*-butylformimidoyl cyanide (2) and hydrolysis<sup>b</sup> of the products (4,5).

Starting material (1)	R <sup>1</sup>	R <sup>2</sup>	Time/h	Product <sup>c</sup>	% Yield <sup>d</sup>	M.p. or b.p./°C <sup>e</sup> (p/mmHg)	Product <sup>c</sup>	% Yield <sup>f</sup>	B.p./°C <sup>e</sup> (p/mmHg)
<b>a</b>	Me	Me	3	(4a)	98	54—55	(7a)	52	130(100)
<b>b</b>	—[CH <sub>2</sub> ] <sub>4</sub> —		8	(4b)	55	58	(7b)	35	140(15)
				(5b)	35	—			
<b>c</b>	—[CH <sub>2</sub> ] <sub>5</sub> —		4	(4c)	35	89—90	(7c)	65	120(2.5)
				(5c)	55	—			
<b>d</b>	Et	Et	9	(4d)	5	—	(7d)	46	140(38)
				(5d)	78	140(13)			
<b>e</b>	Ph	Et	16	(5e)	89	59—60	(7e)	95 <sup>g</sup>	190(13)
<b>f</b>	Ph	H	9	(6)	60	150(0.2)	(8)	57 <sup>h</sup>	150(0.2)

<sup>a</sup> Ratio (1):(2):(3), 1:1:0.1 mol. equiv.; 25—30°C. <sup>b</sup> Hydrolysis of (4), or a mixture of (4) and (5): Cu(OAc)<sub>2</sub>–95% MeOH, heat, 0.5 h. Hydrolysis of (5e) and (6): 0.5 M HCl–95% MeOH, room temp. and reflux, respectively. <sup>c</sup> All new compounds gave satisfactory i.r. and n.m.r. data; most isolated products [including all compounds (7) and (8)] also gave satisfactory microanalytical data. <sup>d</sup> Yield obtained by n.m.r. spectroscopy. <sup>e</sup> B.p. refers to the bath temperature in a 'Kugelrohr' short path apparatus. <sup>f</sup> Overall yield from (1). <sup>g</sup> Yield obtained at room temp. from isolated (5e). <sup>h</sup> Yield obtained under reflux from isolated (6).

**Scheme 1.** Reagents: i, lithium di-isopropylamide; ii, Me<sub>3</sub>SiCl; iii, MeCN; iv, Cu(OAc)<sub>2</sub> or HCl, 95% MeOH.

α-(*t*-butylamino)cyanomethylation of (1) using trimethylsilyl trifluoromethanesulphonate (3) as catalyst, followed by hydrolysis.

The reaction path is illustrated in Scheme 1. The structures and content of mixtures of (4) and (5) were determined by <sup>1</sup>H n.m.r. spectroscopy. In the α-(*t*-butylamino)cyanomethylation, the dehydrocyanated compounds (5) often resulted since the products (4) were susceptible to β-elimination. In particular, bulky α-substituents in (4) appear easily to induce the β-elimination of trimethylsilyl or hydrogen cyanide to afford (5). The reactions of (1e,f) are representative of reactions which give only the β-elimination products (5e,f); compound (5f) possesses an α-hydrogen atom and exists in the form of the prototropic isomer (6) (*E,Z* mixture). Products obtained as a mixture of (4) and (5) were hydrolysed without separation. After completion of the reaction (g.l.c.), the concentrated residue was treated with aqueous potassium carbonate and extracted with di-isopropyl ether. Evaporation gave crude (amino)cyanomethylated esters (4) and/or iminomethylated esters (5) or its isomer (6) in good yields. The reaction conditions, yields, and ratios of the products are summarized in Table 1. Most of the products were purified by recrystallization or distillation *in vacuo*. As summarized in Table 1, α,α-disubstituted α-formylesters (7) and the dimethyl acetal (8) of (7f) were obtained in moderate to good overall yields.

(Amino)cyanomethylation, which permits formylation by successive hydrolyses, has been reported in a few papers involving the use of α-aminoacetonitriles as nucleophiles.<sup>5</sup> The present method provides a new use of compound (2) as an electrophilic species for (amino)cyanomethylation.

Received, 17th September 1984; Com. 1322

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