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

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General α-formylation of α,α-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 α-formylation of esters using alkyl formate as a reagent.[1] Unfortunately, formylation of α,α-disubstituted esters results in low yields of the products,[2] because the reaction equilibrium is unfavourable for compounds lacking an acidic α-hydrogen atom. Ketene silyl acetals (**1**) have been widely utilized as nucleophilic synthons for esters[3] and the reactions occur under mild and non-basic conditions. However, there appears to be only one example in which α-formylated esters were obtained as by-products of the reaction of (**1**) with dichloromethyl methyl ether in the presence of zinc chloride.[4]

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

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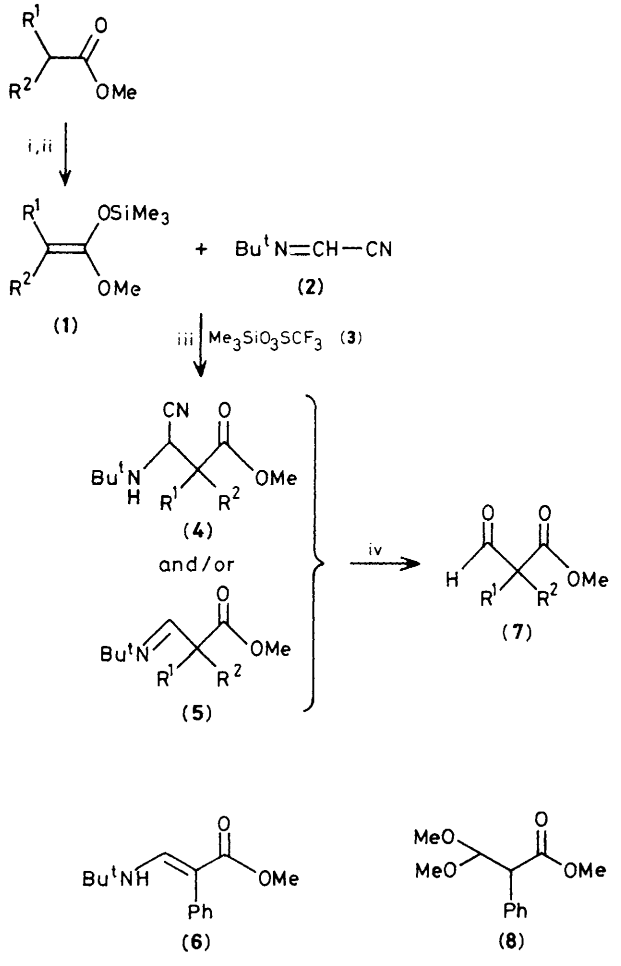
† The reagent (**2**) was prepared in good yield by a modification of the reported *N*-chlorination using *N*-chlorosuccinimide in place of calcium hypochlorite (see ref. 6).

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

Starting material (**1**)	R^1	R^2	Time/h	Product[c]	% Yield[d]	M.p. or b.p./°C[e] (*p*/mmHg)	Product[c]	% Yield[f]	B.p./°C[e] (*p*/mmHg)
a	Me	Me	3	(**4a**)	98	54—55	(**7a**)	52	130(100)
b	$-[CH_2]_4-$		8	(**4b**)	55	58	(**7b**)	35	140(15)
				(**5b**)	35	—			
c	$-[CH_2]_5-$		4	(**4c**)	35	89—90	(**7c**)	65	120(2.5)
				(**5c**)	55	—			
d	Et	Et	9	(**4d**)	5	—	(**7d**)	46	140(38)
				(**5d**)	78	140(13)			
e	Ph	Et	16	(**5e**)	89	59—60	(**7e**)	95[g]	190(13)
f	Ph	H	9	(**6**)	60	150(0.2)	(**8**)	57[h]	150(0.2)

[a] Ratio (**1**):(**2**):(**3**), 1:1:0.1 mol. equiv.; 25—30 °C. [b] Hydrolysis of (**4**), or a mixture of (**4**) and (**5**): $Cu(OAc)_2$–95% MeOH, heat, 0.5 h. Hydrolysis of (**5e**) and (**6**): 0.5 M HCl–95% MeOH, room temp. and reflux, respectively. [c] 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. [d] Yield obtained by n.m.r. spectroscopy. [e] B.p. refers to the bath temperature in a 'Kugelrohr' short path apparatus. [f] Overall yield from (**1**). [g] Yield obtained at room temp. from isolated (**5e**). [h] Yield obtained under reflux from isolated (**6**).



Scheme 1. *Reagents:* i, lithium di-isopropylamide, ii, Me_3SiCl; iii, MeCN; iv, $Cu(OAc)_2$ 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 ^1H 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.[5] The present method provides a new use of compound (**2**) as an electrophilic species for (amino)cyanomethylation.

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