Efficient and Regioselective Cyanosilylation of Cyclohex-2-enone and Other Unsaturated Ketones over Solid Acid and Base Catalysts

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Cyanotrimethylsilane reacts with α,β-unsaturated ketones to afford 1,4- and 1,2-adducts regioselectively in the presence of strongly acidic montmorillonite and strongly basic CaO or MgO, respectively.

Cyanotrimethylsilane (Me_3SiCN) is widely used in organic synthesis instead of HCN.[1] Its addition to carbonyl compounds is usually catalysed either by Lewis acids such as ZnI_2[2] and $AlCl_3$[3] or by anion catalysts like cyanide ion[4] in the homogeneous liquid phase.

Recently, we reported that not only solid acids such as Fe^{3+} ion-exchanged montmorillonite (Fe^{3+}-Mont) but also solid bases such as calcium fluoride and hydroxyapaptite [$Ca_{10}(PO_4)_6(OH)_2$] also promoted cyanosilylation of aldehydes and ketones to give the corresponding cyanohydrin trimethylsilyl ethers in good yields.[5]

We report herein that Me_3SiCN reacts with α,β-unsaturated ketones[6] to give adducts regioselectively which depend on the use of a solid acid or a solid base: 1,4-adducts (silyl enol ethers) are obtained as Michael adducts in the presence of strong solid acids such as Fe^{3+}-Mont and Sn^{4+}-Mont, and 1,2-adducts (silyl ethers) are obtained in the presence of solid bases such as CaO and MgO.

A typical procedure is as follows. The solid catalyst (0.2–0.5 g) was dried at 0.5 Torr for 3 h at 120 °C for cation-exchanged montmorillonite, or 400 °C for hydroxyapatite. CaO and MgO were prepared from $Ca(OH)_2$ and $Mg(OH)_2$ by calcination at 500 °C and 0.5 Torr for 2 h. To a suspension of catalyst and solvent (1 ml) was added a mixture of cyclohex-2-enone (1 mmol) and Me_3SiCN (1.6 mmol) in the same solvent (2 ml) at a given temperature. The mixture was stirred under the conditions shown in Table 1, and the solid catalyst filtered off through a Celite pad. The products were obtained by distillation of the filtrate, and analysed by capillary GC (OV-1.25 m).

Results of the cyanosilylation of cyclohex-2-enone using various catalysts are shown in Table 1. Cyclohex-2-enone reacted with Me_3SiCN to afford three products: the 1,2-adduct **1**, the 1,4-adduct **2** and the bis-adduct **3**.

In the presence of Ni^{2+}-Mont, a relatively weak solid acid, the 1,2-adduct was produced predominantly (run 1). In contrast, the 1,4-adduct was obtained regioselectively in the presence of strong solid acids such as Al^{3+}-, Fe^{3+}-, and Sn^{4+}-Mont (runs 2, 3 and 4). This high regioselectivity may be explicable in terms of the rapid isomerization of the 1,2-adduct into the 1,4-adduct on the strongly acidic catalysts. Indeed, the 1,2-adduct (ratio 98:2) was converted into the 1,4-adduct (yield 92%, ratio 11:89) on Fe^{3+}-Mont in the presence of Me_3SiCN at 0 °C for 1 h.

Table 1 Cyanosilylation of cyclohex-2-enone[a]

Run	Catalyst[b]	Temp/°C (*t*/*h*)	Yield (%) **1 + 2**	(**1**:**2**)	**3**
1	Ni^{2+}-Mont	0(0.3)	86	(61:39)	3
2	Al^{3+}-Mont	0(0.4)	78	(8:92)	8
3	Fe^{3+}-Mont	0(0.4)	84	(8:92)	5
4	Sn^{4+}-Mont	0(0.2)	73	(1:99)	16
5	Sn^{4+}-Mont/MS4A	0(0.2)	94	(0:100)	1
6	ZnI_2	0(0.4)	90	(73:27)	1
7	ZnI_2	40(6.0)	75	(4:96)	11
8	$CF_3SO_3SiMe_3$	0(0.4)	90	(74:26)	0
9	$CF_3SO_3SiMe_3$	40(8.0)	92	(66:34)	1
10	Hydroxyapatite	−45(2.0)	86	(>99:1)	6
11	MgO	−40(0.5)	80	(>99:1)	2
12	CaO	−40(0.3)	87	(>99:1)	2
13	KCN-18-Crown-6	25(2.0)	91	(97:3)	0.2

[a] Cyclohex-2-enone, 1 mmol; Me_3SiCN, 1.6 mmol; CH_2Cl_2 solvent for runs 1–9; PhMe for runs 10–13. [b] Cation exchanged montmorillonite, MS4A, MgO, CaO, 0.2 g; hydroxyapatite, 0.5 g; ZnI_2, $CF_3SO_3SiMe_3$, KCN–18-crown-6, 10 mol%.

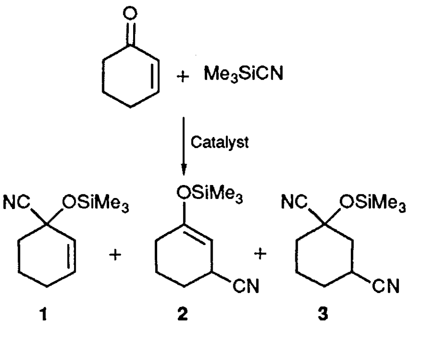
However, with the acid catalysts, the bis-adduct **3** was also produced as a by-product by further cyanosilylation of 3-cyanocyclohexanone formed through hydrolysis of the 1,4-adduct, caused by water contained in the interlayers of montmorillonite. Therefore, in order to suppress the hydrolysis of the 1,4-adduct, molecular sieve 4 Å was used as a drying agent along with Sn^{4+}-Mont. The reaction was carried out after the powdered molecular sieve, pre-dried at 400 °C and 0.5 Torr for 1 h, had been stirred with dried Sn^{4+}-Mont in CH_2Cl_2 for 1 h, whereby the yield of the 1,4-adduct was greatly improved (run 5).

In the presence of homogeneous catalysts (*e.g.* ZnI_2 and $CF_3SO_3SiMe_3$), the 1,2-adduct was produced predominantly under the same conditions (runs 6 and 8). The isomerization barely occurred at 0 °C. In the ZnI_2-catalysed reaction, the 1,4-adduct was obtained selectively at a higher reaction temperature and longer reaction time owing to slow isomerization, compared with the Sn^{4+}-Mont-catalysed reaction (run 7). As for $CF_3SO_3SiMe_3$, the isomerization barely occurred even under reflux (run 9).

The 1,2-adduct was produced regioselectively in reactions using a solid base catalyst such as hydroxyapatite, CaO and MgO. Using basic catalysts, isomerization of the 1,2-adduct did not occur at −40 °C (runs 10, 11 and 12).

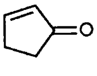
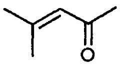
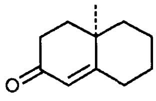
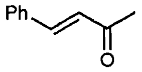
The results of cyanosilylation of various other α,β-unsaturated ketones are shown in Table 2. 4-Methylpent-3-en-2-one and (*R*)-(−)-4,4a,5,6,7,8-hexahydro-4a-methylnaphthalen-2(3*H*)-one reacted with Me_3SiCN to give the 1,2- and 1,4-adducts regioselectively using solid base and solid acid, respectively. In the reaction of cyclopent-2-enone using CaO, the product was a complex mixture of the 1,2-, 1,4- and bis-adducts, because the 1,2-adduct was unstable. Benzylideneacetone, which has a bulky phenyl group at the 4-position, gave the 1,2-adduct predominantly even in the presence of strong acidic catalyst; *i.e.* isomerization was very slow.

Cyanosilylation of (*R*)-(−)4,4a,5,6,7,8-hexahydro-4a-methylnaphthalen-2(3*H*)-one proceeded more quickly at



1 **2** **3**

Table 2 Cyanosilylation of various α,β-unsaturated ketones

Substrate	Catalyst	Solvent	Temp./°C (*t*/h)	Yield (%)	Ratio 1,2 : 1,4
	Fe^{3+}-Mont/MS4A	CH_2Cl_2	−10(0.7)	84	2 : 98
	CaO	PhMe	−45(0.8)	Complex mixture	
	Fe^{3+}-Mont/MS4A	CH_2Cl_2	0(10)	94	1 : 99
	CaO	PhMe	−40(0.7)	93	100 : 0
	Sn^{4+}-Mont/MS4A	CH_2Cl_2	−20(4)	97	1 : 99[a]
	CaO	PhMe	−40(2)	95	100 : 0
	Sn^{4+}-Mont/MS4A	CH_2Cl_2	0(0.2)	97	>99 : 1
	CaO	PhMe	−40(0.5)	97	100 : 0

[a] *cis* : *trans* ratio 28 : 72. Conventional methods: HCN–Et_3Al (tetrahydrofuran, 25 °C, 8 h), quant. yield, *cis* : *trans* 29 : 71;[6e] Me_3SiCN–Et_3Al (PhMe, 25 °C, 20 h), quant. yield, *cis* : *trans* = 31 : 69.[6d]

lower temperatures than conventional methods,[6d,e] and the *cis–trans* ratio of the 1,4-adduct was almost the same as that obtained using conventional methods (Table 2 footnote).

Thus, solid acids and bases were found to be much more effective catalysts for regioselective cyanosilylation of α,β-unsaturated ketones, compared with ordinary homogeneous catalysts.

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