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A one-pot esterification of chiral *O*-trimethylsilyl-cyanohydrins with retention of stereochemistry

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Abstract—Enantiomerically enriched *O*-TMS cyanohydrins have been transformed directly into *O*-acyl-cyanohydrins using various anhydrides or acid chlorides in the presence of catalytic amounts of scandium(III) triflate. The reaction occurs with full retention of stereochemistry and allows the convenient measurement of enantiomeric excesses by chiral HPLC.

Recently, we described a novel method of preparing *O*-TMS cyanohydrins **1** from aromatic aldehydes and TMSCN using asymmetric base catalysis.[1,2] The related Lewis acid catalytic asymmetric trimethylsilylcyanation of aldehydes and ketones has been widely investigated.[3–8] During our work we frequently needed to derivatise the *O*-TMS cyanohydrins generated in order to store the compounds and to improve the peak separation for chiral HPLC analysis. This was initially achieved by the standard, two-step, literature protocol

Table 1. Direct transformation of *O*-TMS cyanohydrins **1** into *O*-acylcyanohydrins **3**

Entry	**1**, R (ee%)	Acylating agent[a]	Reaction time	Ester **3**, yield%[b] (ee%)
1	C_6H_5 (84)	Ac_2O	15 min	98 (83)
2	C_6H_5 (84)	Ac_2O (1 equiv.)	30 min	98 (82)
3	3-MeC_6H_4 (89)	Ac_2O	15 min	98 (85)
4	2-$OMeC_6H_4$ (84)	Ac_2O	15 min	98 (82)
5	*p*-ClC_6H_4 (80)	Ac_2O	15 min	98 (77)
6	*p*-$NO_2C_6H_4$ (55)	Ac_2O	12 h	92 (0)
7	*p*-$NO_2C_6H_4$ (55)	Ac_2O (5 equiv.)	30 min[c]	94 (0)
8	*p*-$CF_3C_6H_4$ (77)	Ac_2O	45 min	98 (78)
9	C_6H_5 (86)	CH_3COCl	1 h	98 (83)
10	C_6H_5 (86)	*t*-BuCOCl	2 h	98 (84)
11	C_6H_5 (83)	PhCOCl	1 h	70 (83)
12	C_6H_5 (84)	$PhCH_2COCl$	2 h	96 (84)
13	$CH_3(CH_2)_6$ (73)	Ac_2O	15 min	98 (73)[d]
14	$CH_3(CH_2)_6$ (73)	$(PhCO)_2O$	3 h	96 (70)
15	$CH_3(CH_2)_6$ (73)	PhCOCl	3 h	98 (71)
16	$C_6H_5CH{=}CH$ (88)	Ac_2O	15 min	98 (88)
17	**4** (49)	Ac_2O	2 h	**5a** 98 (47)
18	**6** (43)	Ac_2O	5 h	**7** 90 (44)

[a] Reaction in acetonitrile at rt. **1**/acylating agent/$Sc(OTf)_3$ = 1:2:0.01, unless stated. [**1**] = 1.0 M^{-1}. Ee measured by HPLC, unless stated (Table 2).
[b] Isolated yield, after flash chromatography (silica gel).
[c] 5 mol% $Sc(OTf)_3$.
[d] Measured by chiral GC.

Keywords: *O*-trimethylsilyl-cyanohydrins; *O*-acyl-cyanohydrins; esterification; scandium triflate; ee measurement.
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of hydrolysis of **1** to give cyanohydrins **2** and then esterification, into **3** using an acid chloride.[6] Herein we disclose that *O*-TMS cyanohydrins **1** can be conveniently, and directly, esterified using anhydrides or acid chlorides in the presence of catalytic amounts of scandium trifluoromethanesulfonate using the methodology previously described for the acylation of various alcohols.[9,10] With such a methodology, we have found that it is possible to avoid aqueous conditions during ester formations that can pose significant practical problems with water-soluble cyanohydrins.[11]

Working in anhydrous conditions, using acetic anhydride in the presence of 1 mol% $Sc(OTf)_3$,[12–14] we were very satisfied to find that this simple and expedient procedure for *O*-acetylation worked for a range of *O*-TMS cyanohydrins and occurred with full retention of stereochemistry (Tables 1 and 2).[15] It has also been demonstrated that esterification by various acid chlorides (phenylacetyl chloride, pivaloyl chloride) may be carried out under such conditions. The procedure also applies to enantiomerically enriched cyanohydrins derived from ketones as in the transformation of **4** to **5** or **6** to **7** (Scheme 1).

Table 2. Measurement of ee of *O*-acylcyanohydrins **3**, **5** and **7**

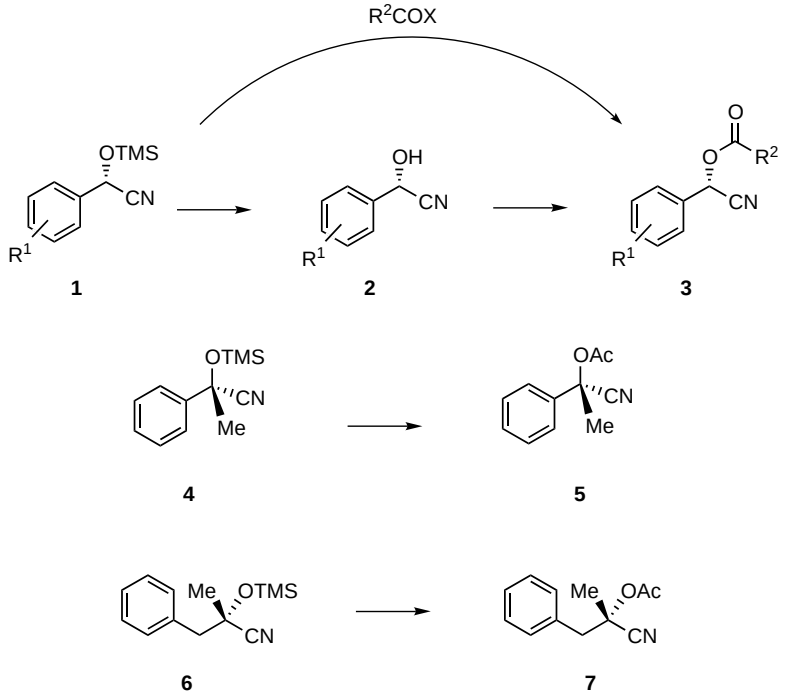
Entry	R^1	R^2	Eluent,[a] hexane/*i*-PrOH	Retention time[b] (min)
1	C_6H_5	Ac	95/5	20.85; 22.63
2	3-MeC_6H_4	Ac	95/5	6.96; 7.87
3	2-$OMeC_6H_4$	Ac	100/1	13.45; 15.13
4	*p*-ClC_6H_4	Ac	90/10	7.97; 9.41
5	*p*-$NO_2C_6H_4$	Ac	98/2/5	23.43; 24.26[d]
6	*p*-$CF_3C_6H_4$	Ac	98/2	9.83; 12.49[c]
7	C_6H_5	*t*-Bu	100/1	12.0; 12.92
8	C_6H_5	PhCO	100/1	11.47; 12.61
9	C_6H_5	$PhCH_2CO$	90/10	8.89; 11.54
10	$CH_3(CH_2)_6$	Ac	GC, 120°C isoth.	104.4; 118.54
11	$CH_3(CH_2)_6$	PhCO	100/1	7.15; 7.87
12	$C_6H_5CH{=}CH$	Ac	98/2	13.43; 16.41
13	**5**		100/1	10.44; 11.88
14	**7**		200/1	16.74; 25.23[c]

[a] HPLC on Chiralcel OD-H, unless entries 5 and 12 ((*S*,*S*)-Whelk-01). Flow: 1 mL min^{-1} except entry 1 (0.4 mL min^{-1}) and entry 7 (0.5 mL min^{-1}).

[b] The major enantiomer is always of (*S*)-configuration, and is the second peak, except in entries 3, 8 and 14.

[c] Isohexane instead of hexane.

[d] Hexane/*i*-PrOH/dichloromethane = 98:2:5. Poor peak separation.



Scheme 1. Direct *O*-acylation of *O*-TMS cyanohydrins.

Conclusion

O-TMS cyanohydrins can be easily transformed into their corresponding esters in a clean and fast one-pot reaction. The process is of interest for analytical purposes and may also be scaled up.[16] This method, using non-aqueous conditions, is especially useful as it delivers *O*-acyl cyanohydrins, which are more stable than their *O*-TMS precursors, and are generally readily analysed by chiral HPLC.

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15. To a solution of *O*-silylated cyanohydrin (1 mmol, 1 equiv.) in 1 mL of acetonitrile was added acetic anhydride (2 mmol, 2 equiv.) and $Sc(OTf)_3$ (4.9 mg, 1 mol%). The resulting solution was stirred for 15 min at rt, then the solvent evaporated and the residue purified by column chromatography (silica gel). Isolated yields are almost quantitative. Enantiomeric excesses of **1** and **3**–**7** were measured by chiral HPLC (Chiralcel OD-H, hexane/isopropanol or chiral GC). Enantioenriched *O*-TMS cyanohydrins **1**, **4** and **6** were obtained by trimethylsilylcyanation of the corresponding aldehydes in the presence of the catalysts described in Refs. 2 and 4.
16. (*S*)-**3** (1.5 g, 7.3 mmol, R = H, 85% ee) in acetonitrile (7.3 mL) was treated with acetic anhydride (14.6 mmol) and $Sc(OTf)_3$ (35.7 mg, 1 mol%). After stirring for 60 min at rt, the solvent was evaporated and the residue purified by column chromatography. The acylated product was isolated in quantitative yield and 85% ee.