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Communications

A Simple and Efficient Synthesis of near Enantiopure β-Hydroxy Nitriles

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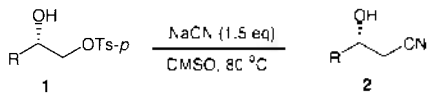
Optically active β-hydroxy nitriles **2** are extremely useful precursors for the synthesis of non-racemic β-hydroxy acids and γ-amino alcohols. They are also of great importance as chiral building blocks for the synthesis of a variety of natural products[1] and chiral drugs[2] because the cyano group can be easily converted into carbonyl and amino groups.[3] For the synthesis of **2**, only few reports including biological methods, such as bio-reduction of β-keto nitriles[4] and enzymatic hydrolysis of acetates of racemic **2**,[5] enantioselective addition of cyanomethylzinc bromide to aldehydes[6] and regioselective ring opening of chiral styrene oxide with acetone cyanohydrin[2c] have been published. Among these, baker's yeast-mediated reduction of β-keto nitriles was generally accompanied by the formation of a significant amount of α-ethylated β-keto nitriles as side-products.[4c-e] and the enantioselectivitity obtained from the same reduction using a fungus cell was highly dependent on the structure of the substrates. For example, the reduction of 2-cyano-1-phenylethanone and 2-cyano-1-(*m*-chlorophenyl)ethanone afforded the corresponding β-hydroxy nitriles with 96% ee and 97% ee respectively, whereas the reduction of 2-cyano-1-(*p*-chlorophenyl)ethanone provided the product β-hydroxy nitrile with only 50% ee.[4a] Enzymatic resolution methods of racemic mixture suffers from providing intrinsic limitation where the maximum yield of one enantiomer from the starting material is only 50%.[5a] In the case of enantioselective cyanomethylation of aldehydes, it requires not only a stochiometic amount of chiral ligand to obtain high enantioselectivity, but also provides only moderate yields (45-82%) due to the low reactivity of the zinc reagent used.[6] Recently, we reported a convenient synthesis of optically active 1,2-diol monotosylates **1** with high optical purities *via* oxazaborolidine-catalyzed borane reduction of α-sulfonyloxyketones.[7] These findings encouraged us to develop a new method for the preparation of optically active **2** starting from **1** by nucleophilic displacement with NaCN.

To determine the optimum reaction conditions, the nucleophilic displacement by reaction of (*S*)-**1** (99% ee) with 1.5 equiv. of NaCN has bee investigated in DMSO at 80 °C (*method A*), in water at 100 °C in the presence of 1 mol% of phase-transfer catalysts (PTC), such as cetyltrimethylammonium bromide and tributylhexadecylphosphonium bromide (method B and C) and in water at 100 °C (method D). Of the methods employed, *method A* provided the best results to give product **2a** in 98% yield. Methods B-D using water as solvent afforded somewhat low yields with the formation of 1-phenyl-1,2-ethanediol as a side-product, although use of PTC increased rate of the reaction dramatically to give the desired product (method B). Enantiomeric excess (ee) of the product **2a** determined by HPLC analysis using Whelk-O1 chiral column showed it to be 99% ee. The results summarized in Table 1 indicate that no racemization occurs under these conditions. Using method A, we carried out cyanation reaction of other optically active 1,2-diol monotosylates **1**. As shown in Scheme 1 and Table 1, all the reaction proceeded smoothly to give optically active β-hydroxy nitriles **2** in high yields.[8] For aromatic analogues **2h-h** bearing *p*-tolyl, *p*-methoxyphenyl, *m*-chlorophenyl, *p*-



1 2

a) R = Ph b) R = 4-MeC_6H_4 c) R = 4-$MeOC_6H_4$ d) R = 3-ClC_6H_4
e) R = 4-ClC_6H_4 f) R = 3,4-$Cl_2C_6H_3$ g) R = 4-FC_6H_4 h) R = 2-Naphthyl
i) R = 2-Thienyl j) R = *t*-Bu k) R = *c*-C_6H_{11}

Scheme 1

Table 1. Preparation of Chiral β-Hydroxy Nitriles **2** from 1,2-Diol Monotosylates **1**

Entry	R	Method	Time	Yield[b] (%)	$[\alpha]_D^{20}$ (*c*, solvent)	Max. values reported	% ee[a]	Config.
1	**2a**	A	<10 min	98	+56.1 (0.9, EtOH)	57.7 (2.6, $CHCl_3$), 96% ee, *S*[4a]	99	*R*
2	**2a**	B	10 min	80	c		99	*R*
3	**2a**	C	60 min	77	c		99	*R*
4	**2a**	D	900 min	57	c		99	*R*
5	**2b**	A	<10 min	96	+65.8 (1.09, $CHCl_3$)	-53.4 (1.5, $CHCl_3$), 82% ee, *S*[4a]	99	*R*
6	**2c**	A	<10 min	97	+69.9 (0.5, $CHCl_3$)	-59.7 (0.6, $CHCl_3$), 83% ee, S[4a]	99	*R*
7	**2d**	A	<10 min	98	+52.1 (0.84, $CHCl_3$)	-56.8 (1.3, $CHCl_3$), 97% ee, *S*[4a]	99[e]	*R*
8	**2e**	A	<10 min	96	+57.6 (0.8, $CHCl_3$)	-52.1 (0.7, $CHCl_3$), 50% ee, [4a]*S*	99	*R*
9	**2f**	A	<10 min	97	+40.5 (0.5, $CHCl_3$)	-37.2 (0.8, $CHCl_3$), 92% ee, *S*[4a]	99[e]	*R*
10	**2g**	A	<10 min	94	+53.7 (0.86, EtOH)		99	*R*[i]
11	**2h**	A	20 min	98	+59.5 (0.5, EtOH)	-52.7 (1.04, EtOH), 87% ee, *S*[6]	99	*R*
12	**2i**	A	<10 min	95		+21.1 (1.18, EtOH)	99[f]	*S*[i,j]
13	**2j**	A	<10 min	90	+48.6 (0.54, $CHCl_3$)	-32.2 (0.6, $CHCl_3$), 83% ee, *S*[4a]	98[g]	*R*
14	**2k**	A	<10 min	93	+9.2 (0.55, $CHCl_3$)	-9.4 (0.9, $CHCl_3$), 88% ee, *S*[4a]	99[h]	*R*

[a]Reaction of (*S*)-**1** with NaCN (1.5 eq) was carried out in the following methods: Method A: DMSO. 80 °C: Method B: n-$C_{16}H_{33}Me_3N^-Br^-$ (1 mol%), H_2O, 100 °C; Method C: n-$C_{16}H_{33}$(n-Bu)$_3P^-Br^-$, H_2O, 100 °C; Method D: H_2O, 100 °C. [b]Isoalted and purified yield. [c]Not measured. [d]Determined by HPLC analysis using a Whelk-O1 column [*iso*-PrOH/hexane: 1/9; flow rate: 0.5 mL/min; detector: 254 nm], unless otherwise indicated. [e]Determined by HPLC analysis using a Chiralcel OD-H column [*iso*-PrOH/hexane: 1/9; flow rate: 1.0 mL/min; detector: 254 nm]. [f]Determined by HPLC analysis of its benzoate using a Chiralcel OD column [*iso*-PrOH/hexane: 1/9; flow rate: 1.0 mL/min; detector: 254 nm]. [g]Determined by GC analysis using a 25 m β-Dex 120 chiral column [105 °C isothermal]. [h]Determined by GC analysis using a 25 m α-Dex 120 chiral column [160 °C isothermal]. [i]Assigned by analogy. [j]By sequence rule.

chlorophenyl, 3,4-dichlorophenyl, *p*-fluorophenyl and 2-naphthyl, near enantiomerically pure products were obtained. We also obtained heterocyclic and aliphatic β-hydroxy nitriles **2i-k** in excellent enantiomeric purity.

In conclusion, we have developed a highly efficient synthetic method for optically active β-hydroxy nitriles which can be widely used as starting materials for preparation of γ-amino alcohols and β-hydroxy acids by employing nucleophilic substitution reaction of chiral 1,2-diol monotosylates with sodium cyanide. It is noteworthy that this method provides near enantiopure β-hydroxy nitriles in aromatic, heterocyclic and aliphatic analogues.

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8. Representative procedure for preparation of **4** (Method A). A mixture of (*S*)-**1** (2 mmol) and sodium cyanide (3 mmol) in DMSO (4 mL) was heated at 80 °C for 10 min and then cooled to room temperature. To this was added water (4 mL) and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined extracts were dried over anhydrous $MgSO_4$, filtered and concentrated. The crude β-hydroxy nitriles (*S*)-**2** obtained were purified further by flash column chromatography on silica gel (230-400 mesh) using ethyl acetate-hexane (1 : 2). All of β-hydroxy nitriles **2** obtained are known compounds except **2g** and **2i**. All spectroscopic data (^1H, ^{13}C NMR and IR) of the known compounds obtained in this study are good agreement with those of literature data.[4a] (*R*)-**2g**: pale yellowish oil (R_f 0.20); yield: 0.31 g (94%); IR (neat): 3429, 2964, 2247, 1606, 1512, 1227 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.62 (br s, 1H), 2.75 (d, 2H, J = 6.10 Hz), 5.04 (t, 1H, J = 6.10 Hz), 7.05-7.15 (m, 2H), 7.32-7.43 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.7, 70.3, 116.4, 117.7, 128.1, 137.5, 161.1. *Anal.* Calcd for C_9H_8FNO: C, 65.45; H, 4.88; N, 8.48. Found: C, 65.55; H, 4.94; N, 8.53; $[\alpha]_D^{20}$ = 53.7 (*c* 0.86, EtOH); HPLC analysis using a Whelk-O1 chiral column (*iso*-PrOH/hexane 1/9; flow rate: 0.5 mL/min; detector: 254 nm) showed it to be 99% ee. [t_R (*R*): 16.05 min; t_R (*S*): 17.95 min]. (*S*)-**2i**: pale yellowish oil (R_f 0.30); yield: 0.29 g (95%); IR (neat): 3411, 2988, 2237, 1658, 1629, 1407, 1063, 1039 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.74 (d, 1H, J = 3.05 Hz), 2.88 (d, 2H, J = 6.41 Hz), 5.30 (m, 1H), 6.99-7.11 (m, 2H), 7.33 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.8, 66.9, 117.6, 125.5, 126.6, 127.8, 145.1. *Anal.* Calcd for C_7H_7NOS: C, 54.88; H, 4.61; N, 9.14; S, 20.93. Found: C, 54.92; H, 4.76; N, 9.09; S, 20.76; $[\alpha]_D^{20}$ = 21.1 (*c* 1.18, EtOH); HPLC analysis of its benzoate using a Chiralcel OD chiral column (*i*-PrOH/hexane 1/9; flow rate: 1.0 mL/min; detector: 254 nm) showed it to be 99% ee. [t_R (*S*): 20.79 min; t_R (*R*): 35.88 min].