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Novel and efficient transformation of α-amino nitrile to α-imino and α-amide nitriles in asymmetric Strecker synthesis

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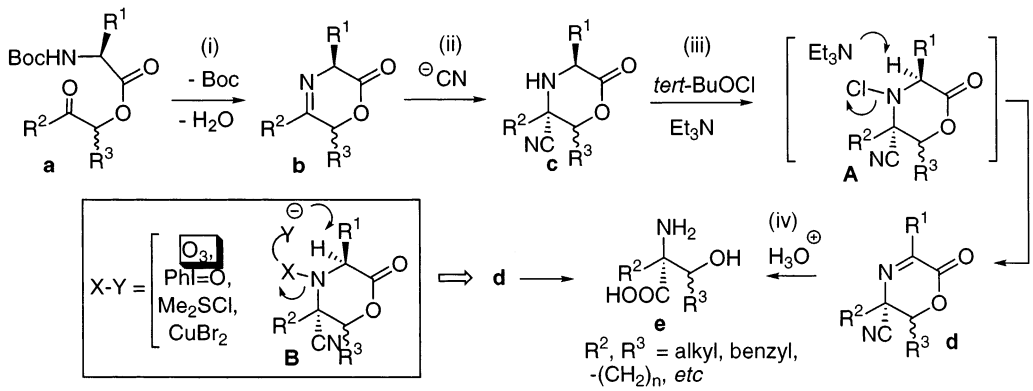
Abstract—Oxidation of α-amino nitrile **4** with ozone gave rise to a mixture of α-imino nitrile **5** and a novel fragmentation product of **6** in one-step. The mixture was converted to a variety of α-substituted α-amino acids **7** in high yields, which enabled the asymmetric transferring Strecker synthesis to be a widely useful method.

The Strecker synthesis is a pivotal methodology to access proteinogenic and non-proteinogenic amino acids. Recently, we have reported an asymmetric version of the Strecker synthesis (asymmetric transferring Strecker synthesis: ATS) which was successfully applied to the synthesis of various classes of β-hydroxy-α-substituted α-amino acids in an optically active form.[1] The synthesis consists of the following sequence of transformations: (i) formation of a cyclic ketimine intermediate **b** from α-acyloxyketone **a** having L- or D-amino acid as the acyloxy group; (ii) stereoselective addition of a cyanide ion to **b** to give an amino nitrile **c**; (iii) oxidative conversion of **c** to an α-imino nitrile **d** and (iv) removal of the chirality transferring amino acid and hydrolysis of the nitrile group under acidic conditions to give an amino acid **e** (Scheme 1). In most cases, these transformations proceeded smoothly to give optically active α-substituted α-amino acids with excellent stereocontrol in satisfactory overall yields. However, we recently observed that the oxidation of sterically congested α-amino nitriles such as **1**, **4b**, and **4e** resulted in a serious decrease in yields or did not give any α-imino nitrile at all (**c** to **d**). These results led us to investigate an alternative method to improve the process (iii). In this report, we describe that ozone oxidation is an efficient protocol for this conversion which accompanied an imine and an unusual fragmentation product, α-amide nitrile, both of which are transformed to the corresponding amino acid in high yields.

The oxidation of α-amino nitrile to α-imino nitrile is often performed by initial *N*-chlorination with *t*-BuOCl and subsequent dehydrochlorination with Et_3N (Scheme 1). However, the latter step is very slow or



Scheme 1.

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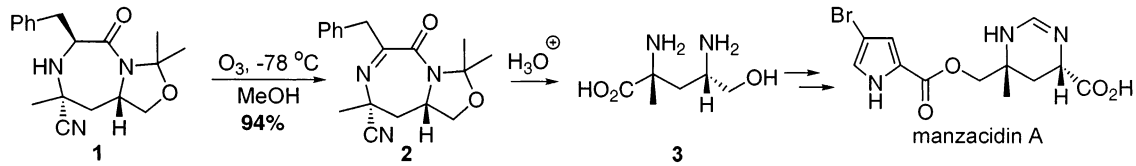
does not proceed at all when the substrates **1**, **4b** and **4e** are employed. Since an external base (**A**) such as Et_3N could not abstract the hydrogen at C2 due mainly to steric reasons, we postulated that a bidentate oxidant would act as the internal base after oxidation of the amino group (**B**). However, treatment of the α-amino nitrile **1** with PhIO, PhSeCl, Me_2SCl, $CuBr_2$, etc.[2] resulted in a complete recovery of **1** where the initial oxidation step in (iii) did not proceed with these reagents. Finally, we examined ozone known as a strong and less bulky oxidant. The oxidation of **1** in methanol at −78°C gave the desired α-imino nitrile **2**, which led to our successful total synthesis of manzacidin A (Scheme 2).[3]

Encouraged by this finding, structurally simple α-amino nitrile **4a** was subjected to the ozone oxidation to optimize the reaction conditions (Table 1, entries 1–7). Contrary to **1**, the reaction afforded a mixture of desired α-imino nitrile[1a,5] and an unexpected α-amide nitrile **6a**.[4] Hydrolysis of **5a** and **6a** with concd hydrochloric acid gave α-methylserine (**7a**) in >99% yield, respectively. Thus, the best yield of the mixture was obtained when ethyl acetate was used as the solvent, and the overall yield from **4a** to **7a** (two-steps) was 97% (entry 3) which was much superior to that attained in the previous three-step conversion (87%).[1a] The products ratio was slightly affected by the solvent and temperature: the use of CH_2Cl_2 afforded **5a** while its

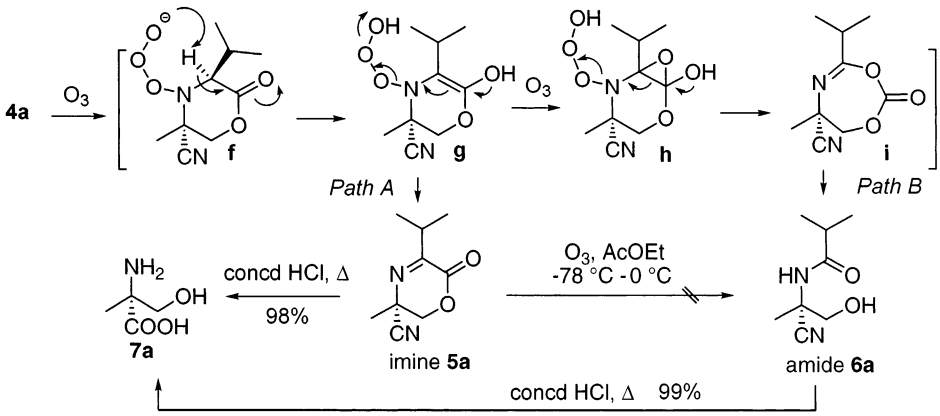


Scheme 2.

Table 1. Conversion of **4** into amino acid **7** by ozone oxidation and subsequent hydrolysis

Entry	Substrates	Conditions	Time (min)	Yield (%)	Ratio of **5**:**6**	Yield (%) of **7** from **4** (two-steps)
1	**4a**	MeOH, −78°C	30	80	1:1	
2	**4a**	MeOH, −40°C	40	32	5:2	
3	**4a**	AcOEt, −78°C	30	98 (86)[a]	3:2	97 (85)[c]
4	**4a**	AcOEt, −40°C	15	99	3:2	
5	**4a**	AcOEt, 0°C	15	99	3:7	
6	**4a**	AcOEt, AcOH (10 equiv.), −78°C	60	93	5:3	
7	**4a**	Dist. CH_2Cl_2, −78°C	120	80	>20:1	
8	**4b**	AcOEt, −78°C	120	83 (61)[a]	1:1	66 (19)[c]
9	**4c**	AcOEt, −78°C	40	98 (80)[a]	3:2	98 (61)[c]
10	**4d**	AcOEt, −78°C	30	94 (55)[a]	2:1	94 (52)[c]
11	**4e**	AcOEt, −78°C	25	93 (0)[a]	2:1	90
12	**4f**	AcOEt, −78°C	95	64 (16)[a,b]	1:1	50–60 (6)[c]
13	**4g**	AcOEt, −78°C	25	73 (43)[a]	1:0	–

[a] Yield (%) of imine **5** using *t*-BuOCl/Et_3N.
[b] Recovery of **4f** (23%).
[c] Yield (%) of **7** via an oxidation using *t*-BuOCl/Et_3N.

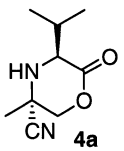
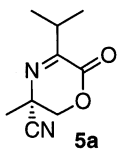
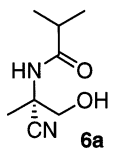
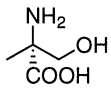
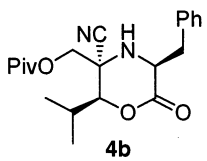
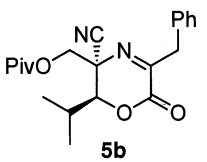
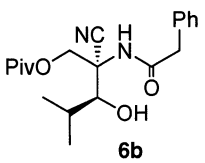
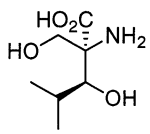
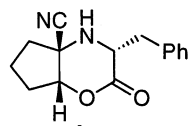
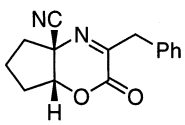
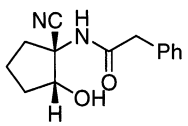
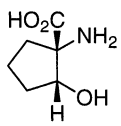
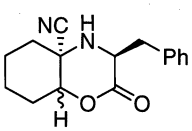
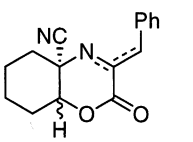
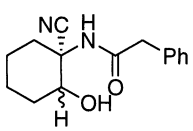
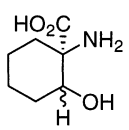
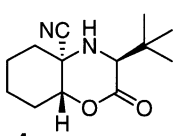
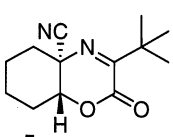
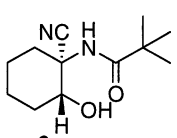
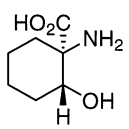
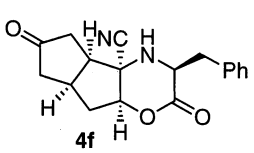
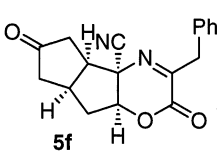
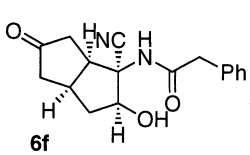
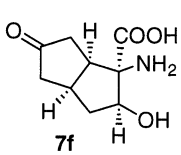
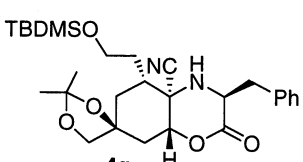
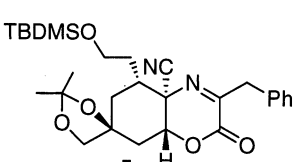


Scheme 3.

yield decreased to 80%, and **6a** was obtained as the major product at the elevated temperature. In addition to these experiments, the isolated imino nitrile **5a** was subjected to the ozone oxidation in ethyl acetate. The reaction resulted in a complete recovery of starting material **5a** even at 0°C, indicating that **6a** was not produced from **5a** under the conditions (Scheme 3). From these results, we propose the following reaction pathway to produce a mixture of **5a** and **6a**: (i) abstraction of the C2 hydrogen from a trioxo species **f** to give an enol **g**; (ii) formation of the imino nitrile **5a** from **g** via an elimination of O_2 and H_2O (path A); (iii) further oxidation of the enol **g** with ozone to give an epoxide **h**, and (iv) carbon–carbon bond cleavage to form a carbonate **i** whose work-up gave **6a** (path B). The less polar solvent would destabilize the enol **g** to prefer the formation of **5a**. On the other hand, oxidation of the enol **g** at 0°C would proceed faster than that performed at lower temperature.

The present method was proven to be extremely effective for the conversion of the other α-amino nitriles **4b–g** (Table 2). Not only mono-cyclic amino nitrile (entry 8) but also bi- and tri-cyclic substrates having sterically bulky substituents (entries 9–12) gave a mixture of the corresponding **5b–f** and **6b–f** in good to excellent yields. The substrate **4g** gave α-imino nitrile **5g**, exclusively. It is noteworthy that the yields of the mixtures including their conversion to the corresponding amino acids **7b–f** were dramatically improved while previous conversions using the *t*-BuOCl/base system were 0% to moderate yields.

Table 2. Structures of α-amino, α-imino, and α-amide nitriles and the corresponding amino acids

α-Amino Nitrile **4a-g**	α-Imino Nitrile **5a-g**	α-Amide Nitrile **6a-f**	α-Amino Acid **7a-f**
 **4a**	 **5a**	 **6a**	 **7a**
 **4b**	 **5b**	 **6b**	 **7b**
 **4c**	 **5c**	 **6c**	 **7c**
 **4d** *cis/trans*=3/2	 **5d** *cis/trans*=1/1	 **6d** *cis/trans*=2/1	 **7d** *cis/trans*=3/2
 **4e**	 **5e**	 **6e**	 *trans*-**7d**
 **4f**	 **5f**	 **6f**	 **7f**
 **4g**	 **5g**		

In summary, the problematic oxidation of α-amino nitrile in ATS was much improved by the use of ozone. This method is advantageous in view of its simple operation and high yield. Furthermore, its utility was exemplified by the conversion of the mixture into various types of optically active β-hydroxy-α-amino acids as well as the total synthesis of natural products possessing an amino group attached to a quaternary carbon center.[2,6]

Acknowledgements

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4. Typical experimental procedure: To a solution of α-amino nitrile **4a** (52 mg, 0.29 mmol) in AcOEt (15 mL) was bubbled O_3 (flow rate of O_2:150 NL/h, which corresponded to 3 g/h of O_3) in a cooling bath (−78°C) for 30 min. The mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt = 4:1) to give **5a** (27 mg, 55%) and **6a** (20 mg, 43%), respectively. Compound **5a**: colorless crystals; mp 45–46°C (Et_2O–hexane); ^1H NMR (300 MHz, $CDCl_3$): δ 4.58 (d, J = 11.7 Hz, 1H), 4.30 (d, J = 11.7 Hz, 1H), 3.24 (sep, J = 6.8 Hz, 1H), 1.71 (s, 3H), 1.17 (d, J = 6.8 Hz, 3H), 1.15 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 153.2, 117.7, 70.4, 52.7, 32.2, 22.4, 19.3, 19.1. Anal. calcd for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71; N, 15.55. Found: C, 60.05; H, 6.76; N, 15.53. IR ($CHCl_3$): 3032, 2988, 2948, 2884, 1756, 1634, 1518, 1466, 1448, 1428, 1400, 1380, 1336, 1284, 1210, 1170, 1114 cm^{-1}; $[\alpha]_D^{23}$ +69.6 (*c* 1.00, $CHCl_3$). Compound **6a**: colorless oil; ^1H NMR (500 MHz, $CDCl_3$): δ 6.55 (br s, 1H), 3.86 (d, J = 11.2 Hz, 1H), 3.80 (d, J = 11.2 Hz, 1H), 2.45 (sep, J = 6.9 Hz, 1H), 1.66 (s, 3H), 1.16 (d, J = 6.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.2, 119.5, 66.9, 52.1, 35.3, 21.9, 19.3, 19.2. FTIR (neat): 3308, 2973, 2937, 2878, 2244, 1663, 1533, 1466, 1387, 1237 cm^{-1}. HRMS (CI) m/z calcd for $C_8H_{14}N_2O_2$ $(M+H)^+$ 171.1134, found 171.1137. $[\alpha]_D^{27}$ +35.4 (*c* 1.33, $CHCl_3$). A solution of imine **5a** (150 mg, 0.83 mmol) in concd HCl (10 mL) was heated at 100°C in a sealed tube for 16 h. The mixture was cooled to room temperature, concentrated in vacuo, and purified using Dowex 50W×4 (elution with H_2O then 1 *N* NH_3) to give α-methylserine (97 mg, 98%): $[\alpha]_D^{21}$ +5.9 (*c* 0.9, H_2O), lit.[1a,5] $[\alpha]_D^{21}$+6.1 (*c* 1.0, H_2O). According to the same procedure, **6a** (48 mg, 0.28 mmol) was hydrolyzed to give **7a** (33 mg, 99%): $[\alpha]_D^{21}$ +5.8 (*c* 0.9, H_2O).
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