Novel synthesis of 3-aminopropionitriles by ring opening of 2-oxazolidinones with cyanide ion

Novel Synthesis of 3-Aminopropionitriles by Ring Opening of 2-Oxazolidinones with Cyanide Ion

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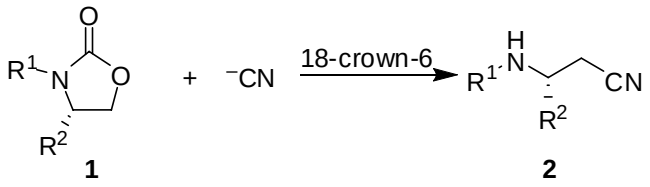
ABSTRACT

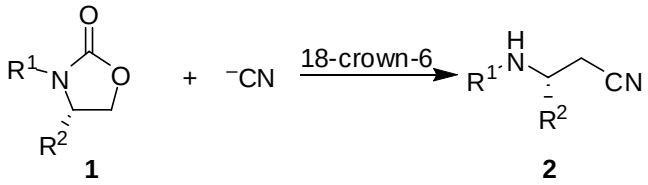


Nucleophilic attack of cyanide ion on the 5-position of 2-oxazolidinones in the presence of 18-crown-6 gave 3-aminopropionitriles.

3-Aminopropionitriles **2** are versatile intermediates in organic synthesis, because the nitrile group can easily be converted into a carboxylic acid or aminomethyl group.[1] Reaction of acrylonitrile with ammonium hydroxide seemed to be the most convenient reaction for the synthesis of non-substituted 3-aminopropionitrile (**2b**),[2] but this method also afforded bis(3-cyanoethyl)amine as a by-product. 3-Aminopropionitrile (**2b**) was

also obtained from 3-chloropropionitrile and liquid ammonia.[3] Many methods for the synthesis of *N*-substituted 3-aminopropionitrile using Michael addition to acrylonitrile have been reported.[4] Herein we report a novel synthesis of 3-aminopropionitriles **2** by ring opening reaction of 2-oxazolidinones **1** with cyanide ion in the presence of 18-crown-6 (Scheme 1). The synthesis of optically active 3-aminopropionitriles is also presented.

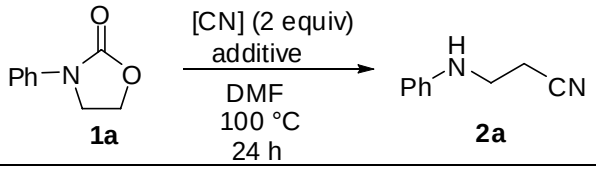
Scheme 1. Formation of **2** by Ring Opening of **1** with Cyanide Ion



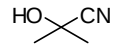
1 **2**

Treatment of 3-phenyl-2-oxazolidinone (**1a**) (R^1 = Ph, R^2 = H in Scheme 1) with KCN (2 equiv) in DMF gave no reaction product after 24 h of heating at 100 °C (Table 1, entry 1). However, the addition of a catalytic amount (0.1 equiv) of 18-crown-6 in the reaction media gave the desired 3-aminopropionitrile **2a** in 34% yield (entry 2). Treatment of **1a** with trimethylsilylcyanide in the presence of tetrabutylammonium fluoride (TBAF) (2.0 equiv) also afforded **2a** in 32% yield (entry 3). Acetone cyanohydrin in the presence of triethylamine gave no desired compound **2a** (entry 4).

Table 1. Reactions of **1a** under Various Conditions



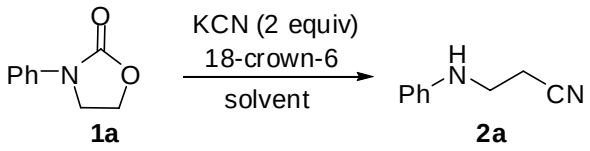
1a **2a**

entry	[CN]	additive (equiv)	yield (%)[a] **2a**	**1a**
1	KCN	none	no reaction	
2	KCN	18-crown-6 (0.1)	34	59
3	TMSCN	TBAF (2.0)	32	20
4		Et_3N (2.0)	no reaction	

[a] Isolated yield.

Table 2 shows the results of reactions of **1a** with KCN (2 equiv) in the presence of 18-crown-6 in various conditions. The use of DMSO or $MeNO_2$ as a solvent did not improve the yield of **2a** compared with that when DMF was used (entries 2 and 3). We found, however, that the yield of **2a** was dramatically improved without using a solvent (entry 4). When an excess (1 or 2 equiv) of 18-crown-6 was used, reaction time was greatly shortened and the yield of **2a** was improved (entries 5 and 6). However, the reaction at a lower temperature (80 °C) took a long time (entry 7), and only a trace amount of product **2a** was obtained when the reaction was carried out at 60 °C (entry 8).

Table 2. Formation of **2a** from **1a** and KCN in the Presence of 18-Crown-6



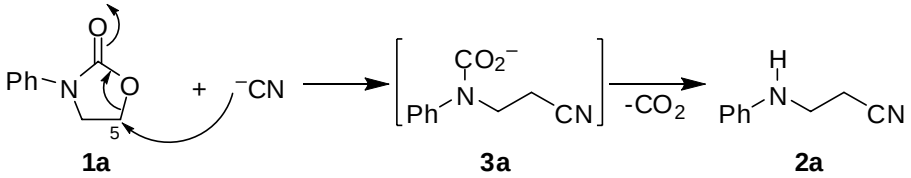
1a **2a**

entry	18-crown-6 (equiv)	solvent	temp. (°C)	time (h)	yield (%)[a]	
					2a	**1a**
1[b]	0.1	DMF	100	24	34	59
2	0.1	DMSO	100	24	32	13
3	0.1	$MeNO_2$	100	24	5	61
4	0.1	neat	100	24	64	17
5	1	neat	100	10	82	2
6	2	neat	100	3	78	19
7	1	neat	80	24	77	9
8	1	neat	60	24	1	97

[a] Isolated yield. [b] Table 1, Entry 2.

Formation of **2a** was explained in terms of a ring opening of oxazolidinone **1a** at the 5-position with cyanide ion followed by a decarboxylation of the resulting carbamate **3a** (Scheme 2).

Scheme 2. Plausible Mechanism for the Formation of **2a** from **1a**

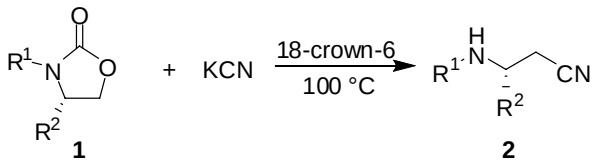


1a **3a** **2a**

An attack of nucleophiles such as aromatic amines[5] or thiolate ions[6] on the 5-position of 2-oxazolidinones **1** has been reported, but, to the best of our knowledge, no example of the use of a carbon nucleophile such as cyanide ion has been reported.

Table 3 shows the results of reactions of other 2-oxazolidinones **1** with KCN (2 equiv) in the presence of 18-crown-6 (1 equiv) without using a solvent.

Table 3. Formation of **2** from **1**



1 **2**

entry	R^1	R^2	**1**	time (h)	**2**	yield (%)[a]	
						2	**1**
1[b]	C_6H_5	H	**1a**	10	**2a**	82	2
2	H	H	**1b**	5	**2b**	13	-
3	Me	H	**1c**	8	**2c**	50	-
4	Bn	H	**1d**	4	**2d**	73	-
5	4-Me-C_6H_4	H	**1e**	12	**2e**	67	6
6	4-MeO-C_6H_4	H	**1f**	20	**2f**	79	5
7	4-Cl-C_6H_4	H	**1g**	5	**2g**	72	13
8[c]	4-NO_2-C_6H_4	H	**1h**	18	**2h**	12	31
9[d]	Bn	Me	**1i**	48	**2i**	63	24
10[e]	Bn	Bn	**1j**	168	**2j**	21	-
11[e]	Bn	C_6H_5	**1k**	24	**2k**	61	-
12	-CH_2-CH_2-CH_2-		**1l**	7	**2l**	65[f]	-

[a] Isolated yield. [b] Table 2, entry 5. [c] At 70 °C. [d] 8 Equiv of KCN was used. [e] 4 Equiv of KCN and 2 equiv of 18-crown-6 were used. [f] Determined by ^{1}H NMR analysis.

The reaction of non-substituted 2-oxazolidinone (**1b**) afforded 3-aminopropionitrile (**2b**) in low yield (entry 2), whereas alkyl-substituted 2-oxazolidinones **1c** and **1d** led to corresponding 3-aminopropionitriles **2c** and **2d** in moderate to good yields, respectively (entries 3 and 4). The reactions of aryl-substituted 2-oxazolidinones **1e-g** with an electron-donating group or a halogen atom provided desired 3-aminopropionitriles **2e-g** in good yields (entries 5-7). *p*-Nitrophenyl-substituted 2-oxazolidinone (**1h**), however, afforded the desired product **2h** in very low yield (entry 8). Ring opening of optically

active 2-oxazolidinones gave the first synthesis of optically active 3-aminopropionitriles. Thus, compounds **1i-l** gave the corresponding 3-aminopropionitriles **2i-l** in moderate to good yields, respectively (entries 9-12).

In conclusion, treatment of 2-oxazolidinones **1** with KCN in the presence of 18-crown-6 resulted in a ring opening reaction to give 3-aminopropionitriles **2**. This reaction proceeds under non-solvent conditions and the experimental procedure is very simple. Further studies directed toward applications to reactions with other carbon nucleophiles are underway in our laboratory.

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Supporting Information Available: Experimental procedure for the synthesis of **2a-l**; ^{1}H and ^{13}C NMR spectra of **2i-l**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and notes

(1) For example, 3-aminopropionitrile (**2b**) was converted to β-alanine by hydrolysis of the nitrile group, see: Ford, J. H. *Org. Synth.* **1947**, *27*, 1.

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