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



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

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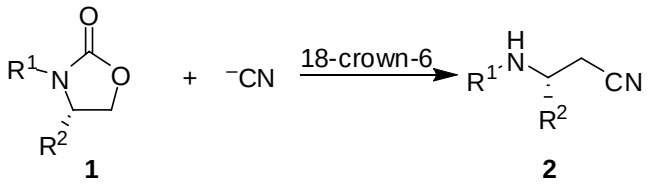
## ABSTRACT

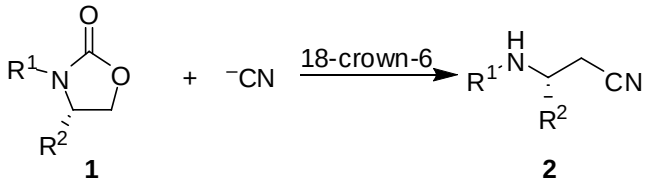



**Nucleophilic attack of cyanide ion on the 5-position of 2-oxazolidinones in the presence of 18-crown-6 gave 3-aminopropionitriles.**

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.

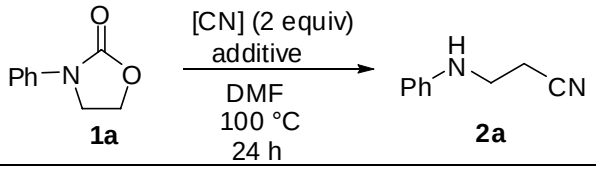
**Scheme 1.** Formation of **2** by Ring Opening of **1** with Cyanide Ion



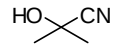

**1** **2**

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



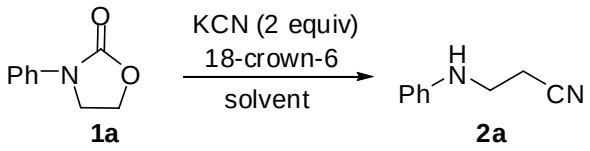

**1a** **2a**

| 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



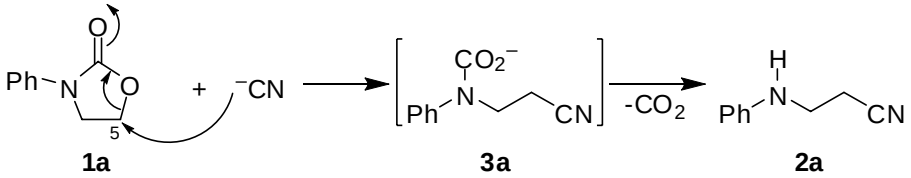

**1a** **2a**

| 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**

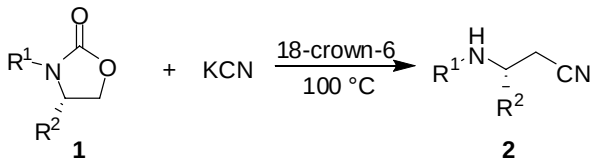



**1a** **3a** **2a**

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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