Tetrahedron Letters 50 (2009) 4857–4858

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

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

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ARTICLE INFO

Article history:
Received 28 April 2009
Revised 30 May 2009
Accepted 5 June 2009
Available online 7 June 2009

ABSTRACT

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

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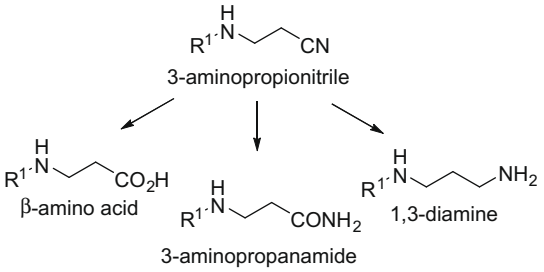
3-Aminopropionitriles are versatile intermediates in organic synthesis, because the nitrile group can easily be converted into a carboxylic acid, amide or aminomethyl group (Scheme 1).[1]

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 the Michael addition to acrylonitrile have been reported.[4] Herein, we report a novel synthesis of 3-aminopropionitriles by ring-opening reaction of 2-oxazolidinones **1** with cyanide ion in the presence of 18-crown-6. The synthesis of optically active 3-aminopropionitriles is also presented.

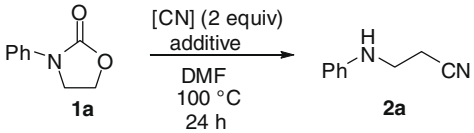
Treatment of 3-phenyl-2-oxazolidinone (**1a**) with KCN (2 equiv) in DMF gave no reaction product after 24 h of heating at 100 °C (Table 1, entry 1). However, the addition of a catalytic amount (0.1 equiv) of 18-crown-6 in the reaction media gave the desired 3-aminopropionitrile **2a** in 34% yield (Table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

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 (Table 2, entries 2 and 3). We found, however, that the yield of **2a** was dramatically improved without using a solvent (Table 2, 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 (Table 2, entries 5 and 6). However, the reaction at a lower temperature (80 °C) took a long time (Table 2, entry 7), and only a trace amount of product **2a** was obtained when the reaction was carried out at 60 °C (Table 2, entry 8).



Scheme 1. Conversion of 3-aminopropionitrile.

Table 1
Reactions of **1a** under various conditions



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	$Me_2C(OH)CN$	Et_3N (2.0)	No reaction	

[a] Isolated yields.

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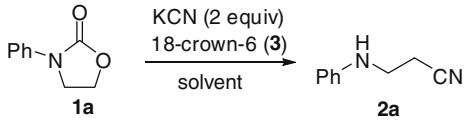
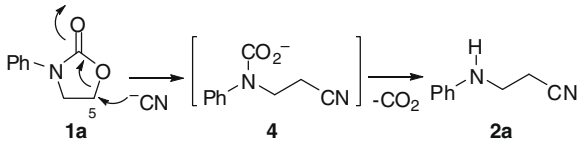
doi:10.1016/j.tetlet.2009.06.014

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



Entry	**3** (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

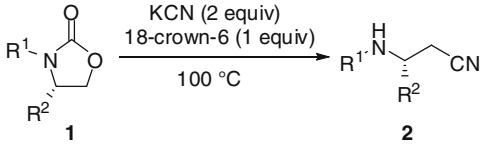
[a] Isolated yields.
[b] Table 1, entry 2.



Scheme 2. Plausible mechanism for the formation of **2a** from **1a**.

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 **4** (Scheme 2). 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.[7]

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



Entry	R^1	R^2	**1**	Time (h)	**2**	Yield[a] (%)	
						2	**1**
1[b]	Ph	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	Ph	**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 ^1H NMR analysis.

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. The reaction of non-substituted 2-oxazolidinone (**1b**) afforded 3-aminopropionitrile (**2b**) in low yield (Table 3, entry 2), whereas alkyl-substituted 2-oxazolidinones **1c** and **1d** led to corresponding 3-aminopropionitriles **2c** and **2d** in moderate to good yields, respectively (Table 3, 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 (Table 3, entries 5–7). *p*-Nitrophenyl-substituted 2-oxazolidinone (**1h**), however, afforded the desired product **2h** in very low yield (Table 3, entry 8). Ring opening of optically active 2-oxazolidinones gave the synthesis of optically active 3-aminopropionitriles. Thus, compounds **1i–l** gave the corresponding 3-aminopropionitriles **2i–l** in moderate to good yields, respectively (Table 3, 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 towards applications to reactions with other carbon nucleophiles are underway in our laboratory.

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

Supplementary data

Experimental procedure for the synthesis of **2a–l**; ^1H and ^{13}C NMR spectra of **2a–l** are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.06.014.

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