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CONVERSION OF OXAZOLINES TO CYANOMETHYL ESTERS WITH PYRIDINIUM HYDROBROMIDE PERBROMIDE IN WATER[1]

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Abstract – Various aromatic and heterocyclic oxazolines were directly converted to respective cyanomethyl esters with pyridinium hydrobromide perbromide in water at room temperature.

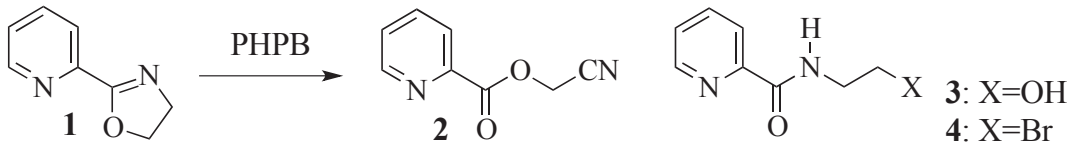
Cyanomethyl esters have been known to be reactive enough to undergo transesterification, amidation, and aminoacylation in organic syntheses.[2] Aminoacylation of RNA derivatives such as 5'-phospho-2'-deoxyribocytidyl riboadenosines (pdCpA)[2c,3] was achieved in high yield by transesterification of the active cyanomethyl esters.[2] The synthesis of tertiary amine-bearing esters[4] and poly(amino)ester dendorimers[2e,5] was similarly explored via active cyanomethyl ester intermediates.

On the other hand, oxazolines have been widely used key intermediates for the synthesis of biologically active compounds and ligands of useful catalysts such as Quinox, Pybox in organic reactions. Therefore, the various syntheses of oxazolines were reported. Many useful organic reactions in the presence of oxazolines were also provided.[6,7] The synthesis of oxazolines from aldehydes with pyridinium hydrobromide perbromide (PHPB) in water was reported in the previous paper.[8a]

Further, the oxidative esterification of aldehydes and Tishchenko-like dimeric esterification of primary alcohols were reported with PHPB in water.[8b] Various heterocyclic and aromatic aldehydes were converted to respective nitriles with PTAB (trimethylphenylammonium tribromide or phenyltrimethyl-ammonium tribromide) in the presence of NH_4OAc.[8c] As cyanomethyl esters were useful for both active and protective groups in organic syntheses,[1-4,9] PHPB or PTAB was expected to be a convenient oxidative reagent for conversion of heterocyclic and aromatic oxazolines to corresponding cyanomethyl esters.[10] We would like to report on the results of our studies concerning the conversion of oxazolines to cyanomethyl esters with PHPB-H_2O.[1]

At first, the reaction of 2-(2'-pyridyl)-1,3-oxazoline (**1**), chosen as a representative heterocyclic oxazoline for this study, was carried out with various molar ratios of PHPB over **1** for obtaining cyanomethyl 2-pyridinecarboxylate (**2**) at room temperature. The results are summarized in Table 1. The reaction of **1**

Table 1. Reaction of 2-(2'-pyridyl)-1,3-oxazoline **1**with PHPB[a]



Run	(Molar ratio / **1**)		Solvent	Time (h)	Product, Yield (%)			
	PHPB	Additive			**2**	**3**	**4**	**1**
1	1.0	--	H_2O	21	22	72	--	--
2	1.0	NaOMe (3.0)	H_2O	17	--	94	--	--
3	1.0	NaOAc (3.0)	H_2O	21	8	86	--	--
4	1.0	NH_4OAc (3.0)	H_2O	22	--	94	--	--
5	1.0	Py (3.0)	H_2O	17	57	25	--	11
6	4.0	Py (4.0)	H_2O	23	92	--	--	--
7	3.0	Py (3.0)	H_2O	22	90	--	--	--[b]
8	4.0	Et_3N (4.0)	H_2O	22	--	89	--	--
9	3.0	Et_3N (3.0)	H_2O	22	--	88	--	--
10	2.0	Py (2.0)	H_2O	14	30	23	--	3[c]
11	4.0	--	H_2O	17	5	49	--	--
12	--	Py (4.0)	H_2O	16	--	6	--	89
13	4.0[d]	Py (4.0)	H_2O	19	73	21	--	--
14	4.0[e]	Py (4.0)	H_2O	18	--	57	--	39
15	4.0	Py (4.0)	hexane	19	8	43	43	--
16	4.0	Py (4.0)	MeOH	16	--	23	47	23
17	4.0	Py (4.0)	MeCN	23	--	--	73	7
18	4.0	Py (4.0)	CH_2Cl_2	19	--	--	93	--

[a] **1**: 0.5 mmol; Solvent: 6 mL; Temp: rt. [b] 2-Pyridinecarbaldehyde: 4%.
[c] 2-Pyridinecarbaldehyde: 36%. [d] PTAB was used insted of PHPB. [e] Pyridinium hydrobromide was used insted of PHPB.

with 1.0 molar ratio of PHPB over **1** gave a mixture of cyanomethyl ester **2** (22%) and *N*-hydroxyethyl-amide (**3**) (72%) in water at room temperature (run 1). HBr generated from PHPB in water was supposed to give amide **3** by hydrolysis of oxazoline **1**. To reduce the generation of HBr, the reaction of **1** was carried out with PHPB in the presence of bases such as NaOMe, NaOAc, NH_4OAc, pyridine. The reaction of **1** in the presence of 3.0 molar ratio of NaOMe, NaOAc, NH_4OAc, afforded *N*-hydroxyethylamide **3** in 86-94% yields by hydrolysis of oxazoline **1** (runs 2-4). As hard acids and bases such as H^+, MeO^-, AcO^- proceeded the conversion of oxazoline **1** to *N*-hydroxyethylamide **3**, the reaction of **1** with PHPB was carried out in the presence of pyridine (Py) as a base. The reaction of **1** with 1.0 molar ratio of PHPB and 3.0 molar ratio of Py over **1** resulted in the formation of cyanomethyl ester **2** (57%), *N*-hydoxyethylamide **3** (25%), and oxazoline **1** (11%) (run 5). The reaction of **1** with 4.0 molar ratio of PHPB-Py was carried out to reduce the generation of *N*-hydoxyethylamide **3** and oxazoline **1**. The yield of cyanomethyl ester **2** was fully satisfactory without generating *N*-hydoxyethylamide **3** (run 6). The reaction of **1** was carried out to examine the optimum amounts of PHPB-Py for conversion of oxazoline **1** to cyanomethyl ester **2**. At 3.0 molar ratio of PHPB-Py, cyanomethyl ester **2** was predominantly afforded in 90% yield (run 7). Further, the reaction of **1** with 3.0 or 4.0 molar ratio of PHPB-Et_3N instead of Py took place to give *N*-hydroxyethylamide **3** in H_2O (runs 8, 9). Py was confirmed to be more useful for conversion of **1** to **2** than other bases such as NaOMe, NaOAc, NH_4OAc, Et_3N. The reaction of **1** with 2.0 molar ratio of PHPB-Py afforded a mixture of cyanomethyl ester **2** (30%), *N*-hydroxyethylamide **3** (23%), and 2-pyridinecarbaldehyde (36%) (run 10). In addition, the reaction of **1** with 4.0 molar ratio of PHPB over **1** in the absence of Py did not give cyanomethyl ester **2** (run 11). The reaction of **1** with 4.0 molar ratio of Py over **1** in the absence of PHPB afforded oxazoline **1** (run 12). Consequently, PHPB and Py were ascertained to be needed 3.0-4.0 molar equivalents over **1** for obtaining **2** in high yield.

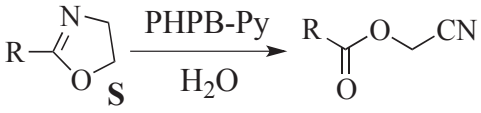
The reaction of **1** in the presence of Py was carried out with PTAB instead of PHPB to test the effect of PHPB under the same reaction conditions. The reaction of **1** with 4.0 molar ratio of PTAB-Py gave a mixture of **2** and *N*-hydroxyethylamide **3** (run 13). The reaction of **1** with pyridinium hydrobromide instead of PHPB in the presence of Py also took place to give a mixture of *N*-hydroxyethylamide **3** and **1** (run 14). Accordingly, PHPB was found to be essential for conversion of **1** to **2** in this system.

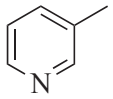
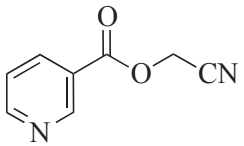
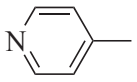
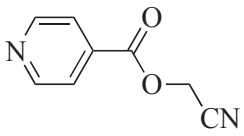
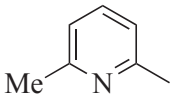
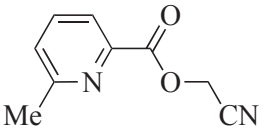
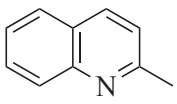
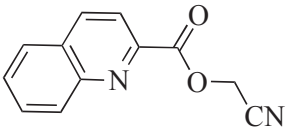
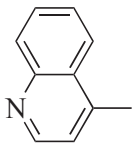
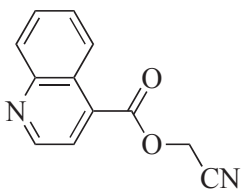
To examine the solvent effect of H_2O, the reaction of **1** with PHPB-Py in hexane, MeOH, MeCN, CH_2Cl_2 was carried out under the same reaction conditions. The reaction of **1** in hexane afforded a mixture of cyanomethyl ester **2** (8%), *N*-hydroxyethylamide **3** (43%), and *N*-bromoethylamide (**4**) (43%) (run 15). The reaction of **1** in MeOH also gave a mixture of *N*-hydroxyethylamide **3** (23%), *N*-bromoethylamide **4** (47%), and oxazoline **1** (23%) (run 16). The reaction of **1** in MeCN took place to give a mixture of *N*-bromoethylamide **4** (73%) and oxazoline **1** (7%) (run 17). *N*-Bromoethylamide **4** was produced in

CH_2Cl_2 (run 18). The reaction of **1** with PHPB in aprotic solvent such as CH_2Cl_2 proceeded to predominantly give *N*-bromoethylamide **4**.[11] H_2O was supposed to be the most suitable for oxidative conversion of oxazoline to cyanomethyl ester with PHPB-Py in the present experiments.

To elucidate the limitations for conversion of oxazolines to cyanomethyl ester, the reaction of various heterocyclic oxazolines was examined with PHPB-Py. The results are shown in Table 2. The respective reaction of 2-(3'-pyridyl)-1,3-oxazoline (**5**), 2-(4'-pyridyl)-1,3-oxazoline (**7**) took place to give corresponding cyanomethyl esters (**6**), (**8**) (runs 1, 2). 2-(6'-Methyl-2'-pyridyl)-1,3-oxazoline (**9**) was similarly converted to cyanomethyl esters (**10**) in moderate yield (run 3). 2-(2'-Quinolinyl)-1,3-oxazoline (**11**) and 2-(4'-quinolinyl)-1,3-oxazoline (**13**) were also converted to corresponding cyanomethyl esters (**12**), (**14**) (runs 4,5).[12]

Table 2. Reaction of heterocyclic oxazolines with PHPB-Py[a]



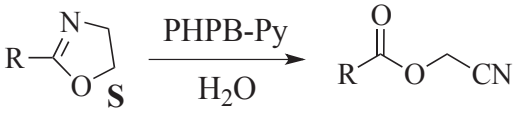
Run	Substrate (**S**) R		Time (h)	Products	Yield (%)	
1		**5**	18		**6**	90
2		**7**	15		**8**	59
3		**9**	17		**10**	93
4		**11**	22		**12**	93
5		**13**	22		**14**	90

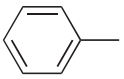
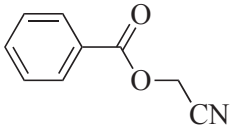
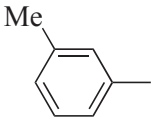
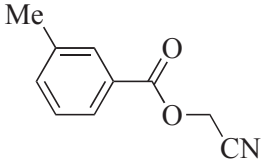
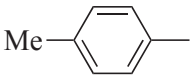
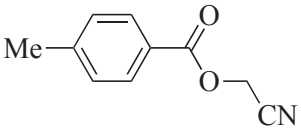
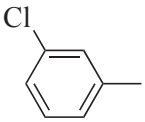
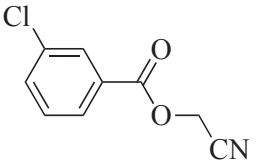
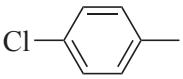
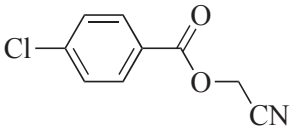
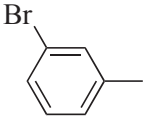
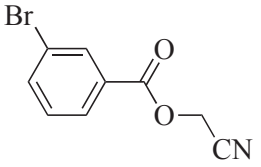
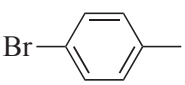
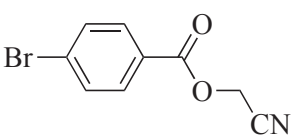
[a] **S**: 0.5 mmol; PHPB: 2.0 mmol; Py: 2.0 mmol; H_2O: 6.0 mL; Temp: rt.

PHPB-Py-H_2O was ascertained to be useful for the conversion of heterocyclic oxazolines to cyanomethyl esters.

In addition, the reaction of a variety of aromatic oxazolines was also carried out to clarify the chemoselectivity by this method at room temperature. The results are summarized in Table 3.

Table 3. Reaction of aromatic oxazolines with PHPB-Py[a]



Run	Substrate (**S**) R		Time (h)	Products		Yield (%)
1		**15**	21		**16**	93
2		**17**	21		**18**	93
3		**19**	22		**20**	90
4		**21**[b]	16		**22**	90
5		**23**	22		**24**	94
6		**25**	22		**26**	93
7		**27**[c]	23		**28**	94

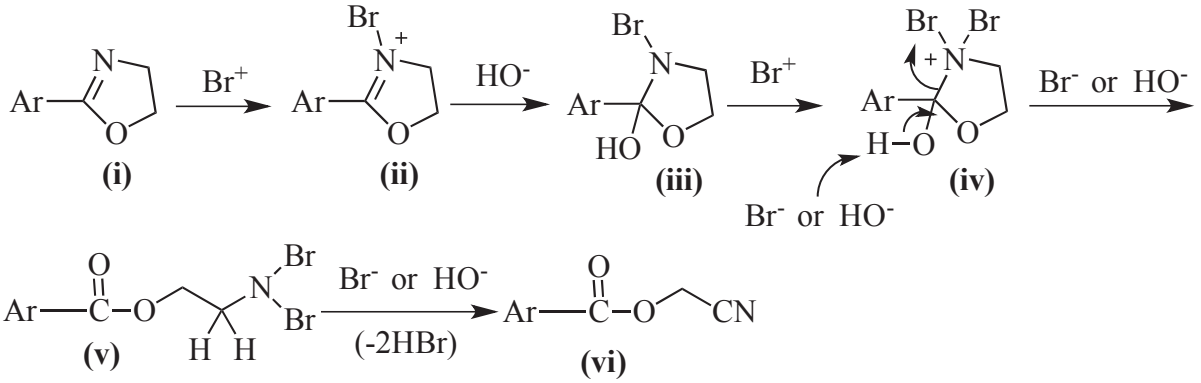
[a] **S**: 0.5 mmol; PHPB: 1.5 mmol; Py: 1.5 mmol; H_2O: 6.0 mL; Temp: rt.
[b] **21**: 0.5 mmol; PHPB: 1.0 mmol; Py: 1.0 mmol.
[c] **27**: 0.5 mmol; PHPB: 2.0 mmol; Py: 2.0 mmol.

2-Phenyl-1,3-oxazoline (**15**) was converted to cyanomethyl ester (**16**) in good yield (run 1). 2-(3'-Methylphenyl)-1,3-oxazoline (**17**), 2-(4'-methylphenyl)-1,3-oxazoline (**19**) were converted to respective cyanomethyl esters (**18**), (**20**) in moderate yields (runs 2,3). The reaction of 2-(3'-chlorophenyl)-1,3-oxazoline (**21**), 2-(4'-chlorophenyl)-1,3-oxazoline (**23**) afforded corresponding cyanomethyl esters (**22**), (**24**) (runs 4, 5). 2-(3'-Bromophenyl)-1,3-oxazoline (**25**), 2-(4'-bromophenyl)-1,3-oxazoline (**27**) were also converted to corresponding cyanomethyl esters (**26**), (**28**) in good yields (runs 6, 7).[13] The conversion of aromatic oxazolines to cyanomethyl esters by PHPB-Py-H_2O was not rested on electron donating or withdrawing substituents on aromatic ring. PHPB-Py-H_2O was also convenient for preparation of cyanomethyl esters from aromatic oxazolines.

The above mentioned observations suggested that the conversion of oxazolines to cyanomethyl esters with PHPB-Py-H_2O was proceeded as follows illustrated in eq. 1, eq. 2, and Scheme 1. First, the combination of PHPB and H_2O appeared to generate HO^-Br^+, HBr, and pyridinium hydrobromide (PyHBr). Nitrogen of oxazoline (**i**) was attacked by Br^+ and lead to ammonium bromide (**ii**). Ammonium bromide (**ii**) attacked by HO^- was transformed into (**iii**). Successive bromination of (**iii**) by Br^+ gave intermediate (**iv**). Oxidative esterification step was proposed to enable for feasible route (**iv** → **v**) in Scheme 1. Finally, dehydrobromination of (**v**) by HO^- or Br^- produced cyanomethyl ester (**vi**). Py neutralized an additional formation of HBr (eq. 2).

$$\text{PHPB} + H_2O \longrightarrow HO^-Br^+ + \text{HBr} + \text{PyHBr} \quad \text{(eq. 1)}$$

$$\text{HBr} + \text{Py} \longrightarrow \text{PyHBr} \quad \text{(eq. 2)} \qquad \text{PHPB: } [\text{PyH}]^+Br_3^-\text{; Py: pyridine}$$



Scheme 1

In conclusion, PHPB-Py-H_2O was confirmed to be an alternative oxidative procedure for the conversion of various heterocyclic and aromatic oxazolines to cyanomethyl esters without generating hydroxyethylamides and overoxidizing to carboxylic acids.

EXPERIMENTAL

IR spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with a JEOL JNM-EX270 spectrometer at room temperature and the chemical shifts (δ) were given relative to internal standard $SiMe_4$ in $CDCl_3$. Anal were run on a Yanagimoto MT-6.

Typical procedure

To a solution of 2-(2'-pyridyl)-1,3-oxazoline (**1**, 37 mg, 0.25 mmol) and pyridine (80 μL, 1.0 mmol) in H_2O (6 mL), was added pyridinium hydrobromide perbromide (320 mg, 1.0 mmol) at room temperature. After stirring for 23 h at rt, the reaction mixture was treated with 0.5 M aq $Na_2S_2O_3$ (10 mL), 1.0 M $NaHCO_3$ (15 mL) and extracted with EtOAc (60 mL). The organic layer was washed with 0.5 M aq $Na_2S_2O_3$ and successively washed with saturated aq NaCl, and dried over $MgSO_4$. After removal of solvent in vacuo, the residue was purified by column chromatography on silica gel (Wako C-200) with CCl_4, CCl_4-$CHCl_3$ (2:1 v/v). Cyanomethyl 2-pyridinecarboxylate (**2**, 38 mg, 0.23 mmol) was obtained in 92% yield.

Cyanomethyl 2-pyridinecarboxylate (2): IR (KBr, cm^{-1}) 3085, 2984, 2944, 2850, 2739, 1736, 1588, 1573, 1509, 1441, 1434, 1379, 1307, 1292, 1271, 1245, 1220, 1150, 1092, 1043, 999, 985, 916, 819, 750, 710, 699. ^{1}H NMR ($CDCl_3$) δ 5.04 (2H, s), 7.55 (1H, t, *J* = 8.1 Hz), 7.91 (1H, t, *J* = 8.1 Hz), 8.19 (1H, d, *J* = 8.1 Hz), 8.80 (1H, d, *J* = 8.1 Hz). ^{13}C NMR ($CDCl_3$) δ 49.39, 113.99, 125.92, 128.04, 137.44, 145.70, 150.00, 143.73, 163.45. *Anal*. Calcd. for $C_8H_6O_2N_2$: C, 59.25; H, 3.72; N, 17.28. Found: C, 59.25; H 3.83; N, 17.12.

Pyridine-2-*N*-(2-hydroxyethyl)carboxamide (3): IR (neat, cm^{-1}) 3378, 3059, 2935, 2878, 1661, 1590, 1569, 1537, 1465, 1435, 1361, 1290, 1246, 1220, 1170, 1147, 1065, 997, 913, 820, 750, 693, 621. ^{1}H ($CDCl_3$) δ 3.66 (2H, t, *J* = 5.4 Hz), 3.86 (2H, t, *J* = 5.4 Hz), 7.44 (1H, m), 7.86 (1H, t, *J* = 8.1 Hz), 8.20 (1H, d, *J* = 8.1 Hz), 8.55 (1H, d, *J* = 5.4 Hz). ^{13}C NMR ($CDCl_3$) δ 42.53, 62.48, 122.29, 126.33, 137.44, 148.14, 149.71, 165.55. *Anal*. Calcd for $C_8H_{10}O_2N_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.95; H, 6.04; N, 16.97.

Pyridine-2-*N*-(2-bromoethyl)carboxamide (4): IR (KBr, cm^{-1}) 3338, 3069, 3057, 3037, 2977, 2948, 1663, 1627, 1591, 1570, 1532, 1522, 1467, 1439, 1431, 1404, 1353, 1303, 1294, 1284, 1225, 1183, 1163, 1140, 1085, 1072, 1042, 969, 952, 855, 820, 751. ^{1}H NMR ($CDCl_3$) δ 3.59 (2H, t, *J* = 5.4 Hz), 3.91 (2H, t, *J* = 5.4 Hz), 7.45 (1H, dd, *J* = 8.1, 5.4 Hz), 7.86 (1H, t, *J* = 8.1 Hz), 8.18 (1H, d, *J* = 8.1 Hz), 8.58 (1H, d, *J* = 5.4 Hz). ^{13}C NMR ($CDCl_3$) δ 31.86, 41.09, 122.24, 126.37, 137.35, 148.19, 149.39, 164.48. *Anal*. Calcd. for $C_8H_9ON_2Br$: C, 41.94; H, 3.96; N, 12.23. Found: C, 42.04; H 3.98; N, 12.20.

Cyanomethyl 4-pyridinecarboxylate (8): IR (neat, cm^{-1}) 2997, 2959, 1737, 1596, 1563, 1494, 1431,

1408, 1366, 1326, 1294, 1275, 1260, 1222, 1211, 1124, 1063, 993, 983, 955, 853, 759, 702, 676, 664. ^{1}H NMR ($CDCl_3$) δ 5.01 (2H, s), 7.87 (2H, d, *J* = 8.1 Hz), 8.85 (2H, d, *J* = 8.1 Hz), ^{13}C NMR ($CDCl_3$) δ 49.34, 113.75, 122.88, 135.33, 150.96, 163.76. *Anal.* Calcd. for $C_8H_6O_2N_2$: C, 59.25; H, 3.72. Found: C, 58.89; H, 3.69.

Cyanomethyl 2-(6-methyl)pyridinecarboxylate (10): IR (neat, cm^{-1}) 2997, 2954, 1733, 1691, 1593, 1458, 1437, 1378, 1306, 1268, 1258, 1236, 1185, 1161, 1122, 1084, 1034, 1012, 994, 984, 916, 885, 830, 783, 762, 713, 669. ^{1}H NMR ($CDCl_3$) δ 2.68 (3H, s), 5.03 (2H, s), 7.42 (1H, d, *J* = 8.1 Hz), 7.78 (1H, t, *J* = 8.1 Hz), 8.00 (1H, d, *J* = 8.1 Hz). ^{13}C NMR ($CDCl_3$) δ 24.58, 49.31, 114.11, 123.19, 127.84, 137.32, 145.48, 159.52, 163.89. *Anal*. Calcd. for $C_9H_8O_2N_2$: C, 61.35; H, 4.57; N, 15.90. Found: C, 61.16; H, 4.62; N, 15.73.

Cyanomethyl 4-quinolinecarboxylate (14): IR (neat, cm^{-1}) 2976, 1739, 1584, 1507, 1460, 1441, 1369, 1268, 1249, 1181, 1147, 1134, 1078, 1034, 1016, 969, 884, 860, 793, 774. ^{1}H NMR ($CDCl_3$) δ 5.09 (2H, s), 7.72 (1H, t, *J* = 8.1 Hz), 7.83 (1H, t, *J* = 8.1 Hz), 7.98 (1H, d, *J* = 5.4 Hz), 8.20 (1H, d, *J* = 8.1 Hz), 8.79 (1H, d, *J* = 8.1 Hz), 9.08 (1H, d, *J* = 5.4 Hz). ^{13}C NMR ($CDCl_3$) δ 49.25, 113.97, 122.73, 124.79, 125.08, 128.92, 130.14, 130.31, 131.80, 149.21, 149.67, 164.49. *Anal*. Calcd. for $C_{12}H_8O_2N_2$: C, 67.91; H, 3.80; N, 13.20. Found: C, 67.53; H, 3.87; N, 12.99.

Typical procedure of aromatic oxazoline

The reaction of 2-(3'-bromophenyl)-1,3-oxazoline (**25**) (904 mg, 4 mmol) was carried out as follows: To a solution of **25** (904 mg) in H_2O (50 mL), were added pyridine (0.96 mL, 12 mmol) and PHPB (3.84 g, 12 mmol). After stirring for 22 h at rt, the reaction mixture was treated with 0.5 M aq $Na_2S_2O_3$ (30 mL), 1.0 M aq $NaHCO_3$ (50 mL) and extracted with EtOAc (80 mL). The organic layer was washed with 0.5 M aq $Na_2S_2O_3$ (30 mL), successively saturated aq NaCl (50 mL), and dried over $MgSO_4$. After removal of solvent in vacuo, the residue was purified by column chromatography (ϕ 20 mm, L 120 mm) on silica gel (Wako C 200) with CCl_4, CCl_4 and $CHCl_3$ (2:1 v/v). Cyanomethyl 3-bromobenzoate (**26**) (762 mg, 79%) was obtained.

Cyanomethyl 3-bromobenzoate (26): IR (neat, cm^{-1}) 3070, 3011, 2958, 1738, 1593, 1571, 1474, 1426, 1367, 1281, 1251, 1168, 1118, 1082, 1069, 998, 915, 818, 744, 724, 671, 652. ^{1}H NMR ($CDCl_3$) δ 4.97 (2H, s), 7.37 (1H, t, *J* = 8.1 Hz), 7.76 (1H, d, *J* = 8.1 Hz), 7.99 (1H, d, *J* = 8.1 Hz), 8.20 (1H, brs). ^{13}C NMR ($CDCl_3$) δ 49.06, 114.12, 122.73, 128.55, 129.71, 130.26, 132.93, 137.09, 163.66. *Anal*. Calcd for $C_9H_6O_2NBr$: C, 45.02; H, 2.51; N, 5.83. Found: C, 44.89; H, 2.53; N, 5.80.

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11. (a) Esterification of aldehydes and ethyleneglycol with PHPB in CH_2Cl_2 afforded bromoethyl esters;

T. Aoyama, T. Takido, and M. Kodomari, *Tetrahedron Lett*., 2005, **46**, 1989; (b) Esterification of aldehydes and ethyleneglycol with PHPB in H_2O took place to give hydroxyethyl esters; S. Sayama and T. Onami, *Synlett*, 2004, 2739.

12. The reaction of 2-(3'-quinolinyl)-1,3-oxazoline took place to give cyanomethyl ester in 10-20% yields accompanied by recovered oxazoline under the same reaction conditions.
13. *ortho*-Substituted 2-phenyl-1,3-oxazolines were not fully converted to respective cyanomethyl esters.