A FACILE ONE-POT SYNTHESIS OF 4-ALKOXY-1,3-BENZENEDICARBONITRILE

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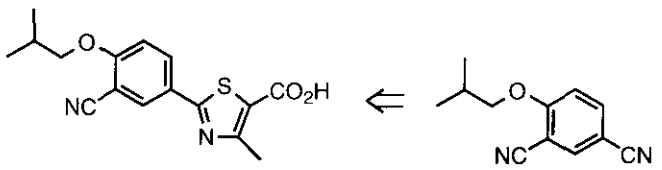
Abstract — 2-(3-Cyano-4-isobutoxyphenyl)-4-methylthiazole-5-carboxlic acid (TEI-6720) was prepared. The introduction of cyano group to 4-nitrobenzonitrile with KCN in dry DMSO followed by quenching with alkyl halide afforded the key intermediates, 4-alkoky-1,3-benzenedicarbonitriles, in good yield. The reaction was completed in dry DMSO, while no reaction occurred in dry DMF. This observation can be suggested by the participation of DMSO in the reaction.

Recent papers showed that TEI-6720, 2-(3-cyano-4-isobutoxyphenyl)-4-methylthiazole-5-carboxylic acid, is a promising remedy for hyperuricemia and gouty arthritis because this compound inhibits xanthine oxidase (IC_{50} = 1.4–2.2 nM) much stronger than allopurinol, a traditional xanthine oxidase inhibitor. [1,2] TEI-6720 possesses characteristic thiazole and trisubstituted benzene ring. In general, 4-methylthiazole-5-carboxylic acids are prepared by annulation of 2-chloroacetoacetate with thioamide derived from corresponding nitrile. [3] Therefore, 4-isobutoxy-1,3-benzenedicarbonitrile (**2b**) was thought to be a tentative intermediate of TEI-6720. However, the general method for the preparation of 4-alkoky-1,3-benzenedicarbonitrile is not known.



TEI-6720 **2b**

Since aryl nitriles are usually prepared by the substitution reaction from corresponding aryl halide, [4] aryl amine, [5] or aryl aldoxime, [6] prior introduction of the leaving group was thought to be necessary. Direct introduction of cyano moiety to an unsubstituted site on the phenyl ring by photoinduced reaction was also reported. [7] However, the site of introduction of cyano group seems difficult to predict. Gorvin succeeded in the preparation of 4-benzoyl-2-cyanophenol *via* hydroxylation-cyanation reaction using

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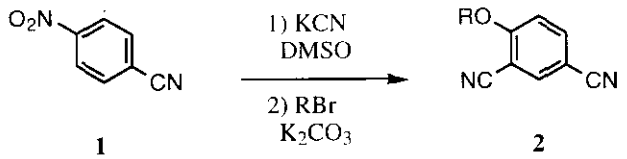
This paper is dedicated to Prof. K. Nakanishi on the occasion of his 75th birthday.

KCN from 4-benzoylnitrobenzene. [8] Although the reaction mechanism was not detailed, this method was of great interest because it seems to be applicable for the objective to prepare **2b**. Direct introduction of cyano group to the unsubstituted site on the ring was performed regiospecifically. Unfortunately, the preparation of 4-hydroxy-1,3-benzenedicarbonitrile was not described in detail, and the treatment with acid after the reaction would not be favorable because of the possible formation of poisonous hydrogen cyanide derived from KCN. Disclosed here is a safe, effective, and improved one-pot synthesis of novel 4-alkoxy-1,3-benzenedicarbonitriles. Further, TEI-6720 was prepared in short steps by use of this reaction. In addition, I would like to discuss the mechanism of this hydroxylation-cyanation reaction.

The typical experimental procedure is simple: A solution of 4-nitrobenzonitrile (1 equivalent) and KCN (1.5 equivalent) in dry DMSO was heated at 100 °C with stirring for 1 h. The mixture was cooled to 80 °C, then K_2CO_3 (0.5 equivalent) and alkyl halide (2-4 equivalent) were introduced to the reaction mixture. Further stirring continued for 1 – 24 h at rt. – 80 °C until the reaction was accomplished. Basic workup and subsequent purification by silica gel column chromatography gave novel 4-alkoky-1,3-benzenedicarbonitriles in good yield.

Table 1. One-pot Preparation of 4-Alkoxy-1,3-benzenedicarbonitrile



1 **2**

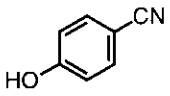
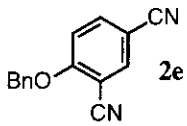
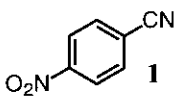
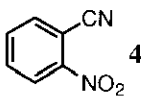
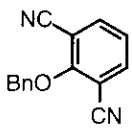
Product	R	temp.(°C) [a]	time (h) [a]	yield(%)
2a	Et	70	2	70
2b	*i*-Bu	70	6	73
2c	*n*-Octyl	70	2	73
2d	$EtO(CH_2)_2$	70	6	50
2e	Bn	25	3	85
2f	$2\text{-}C_{10}H_7CH_2$	25	3	80

[a] Reaction condition of the 2nd step

The results are summarized in Table 1. Yields were fairly good and no appreciable amount of by-products was detected except for **2d**, where the lower yield in **2d** may be explained by concurrent elimination reaction in the 2nd step. Since benzylation (**2e**) and naphthylmethylation (**2f**) were fast, the

reactions were performed at rt. When K_2CO_3 was not added, the reaction was not completed, and 4-hydroxy-1,3-benzenedicarbonitrile (**3**) was recovered (data not shown) owing to the low basicity of the resulting solution of formed KNO_2 and remaining KCN.

Table 2. Miscellaneous Reactions with KCN Followed by Benzylation [a]

Run	Starting Compd	Solvent	Product(s)	Yield (%)
1		dry DMSO	 **2e**	0
2	 **1**	dry DMSO	**2e**	85
3	**1**	dry DMF	**2e**	0
4	**1**	dryDMF + 2 equiv. H_2O	**2e**	39
5	 **4**	dry DMSO	**2e** +  **5** (55 : 45)	95

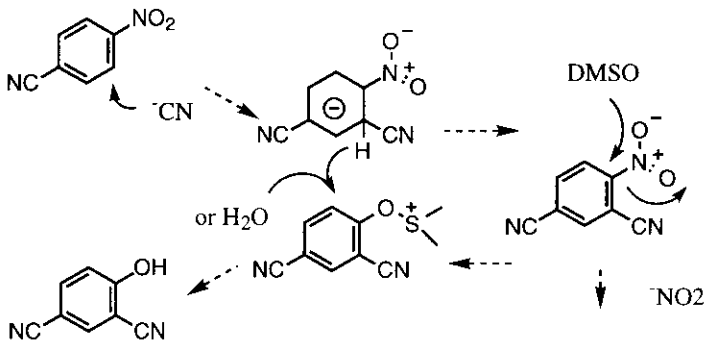
[a] All experiments were carried out with KCN (1.5 equiv.) at 100°C for 1 h followed by cooling to ambient temperature and treatment with benzyl bromide.

The reaction of 4-nitrobenzonitrile toward 4-alkoxy-1,3-benzenedicarbonitrile consists of tandem hydroxylation-cyanation and subsequent alkylation. As the mechanism of the former reaction is not known, some related reactions with KCN were carried out followed by quenching with benzyl bromide (Table 2). 4-Hydroxybenzonitrile did not undergo cyanation which indicates that NO_2 moiety plays a pivotal role in this reaction and that the cyanation proceeds before the hydroxylation of NO_2 (Run 1). Noteworthy is the fact that the reaction in dry DMF instead of DMSO resulted in the recovery of **1** (Run 3), while the reaction was completed in dry DMSO to give **2e** in high yield (Run 2). The reaction was retrieved partly when water (2 equivalents) was introduced to the reaction mixture in DMF (Run 4), suggesting that the remaining H_2O in DMF may be the oxygen source. However it seems strange that **2e** was obtained in high yield when anhydrous DMSO was used (Run 2). Additive water did not affect the reaction when DMSO was used (data not shown). Therefore, DMSO itself presumably plays an

important role in this reaction.

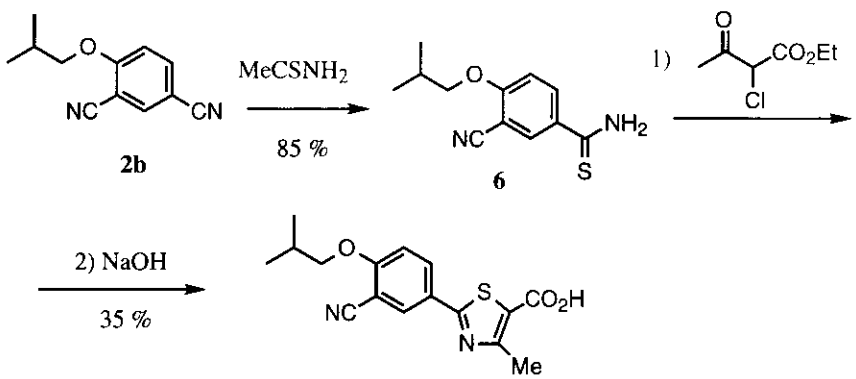
2-Nitrobenzonitrile (**4**) was used as a starting compound instead of 4-nitrobenzonitrile in order to evaluate the regioselectivity of this reaction. The formation of *para* product (**5**) indicates that neighboring-nitro-assistance was probably unnecessary for the reaction (Run 5). It seems reasonable that the nitro group had a stronger orientation effect than the cyano group in the cyanation reaction.

Scheme 1



These results led the reaction mechanism assumed (Scheme 1). Cyano anion attacked the site adjacent to the nitro group owing to the stronger orientation effect of nitro moiety. Immediately after the hydride was removed, disubstituted cyano group enhanced the leaving potential of the nitro moiety, so that inactive DMSO was forced to substitute for nitro moiety. Subsequent hydrolysis or reduction by hydride gave rise to the formation of dicyanophenol. Final alkylation was carried out with alkyl halide in alkali condition.

Scheme 2



The conversion of 4-nitrobenzonitrile (**1**) to alkoky-1,3-benzenedicarbonitrile allowed the development of a convenient access to 2-(4-alkoxy-3-cyanophenyl)-4-methylthiazole-5-carboxylic acid derivatives,

xanthine oxidase inhibitors. As a representative example, the efficient synthesis of TEI-6720 is outlined in Scheme 2. The resulting **2b** was treated with thioacetamide [9] followed by cyclization with chloroacetoacetate [10] and hydroxylation to afford TEI-6720 [1,2] in 60% yield. Similar conversion of **2d** led to 2-(4-ethoxyethoxy-3-cyanophenyl)-4-methylthiazole-5-carboxylic acid which showed XOD inhibitory activity with an IC_{50} of 1.9 nM. This result implies that a series of 2-(4-alkoxy-3-cyanophenyl)-4-methylthiazole-5-carboxylic acids generally possess strong xanthine oxidase inhibitory activity.

EXPERIMENTAL SECTION

General

NMR spectra were recorded on a JEOL EX-270 fourier transform spectrometer, using tetramethylsilane as an internal standard. The FT-IR spectra were determined on a JASCO 5300 system in a KBr powder. Purification by medium pressure liquid chromatography was carried out with DAISO IR-60 silica gel. Melting points were measured on a Yanako MP-S3 apparatus. HRMS were obtained on a HITACHI M-80 B spectrometer. Commercially available reagents and solvents were used as supplied unless otherwise stated. DMSO and DMF were distilled over calcium hydride and stored on molecular sieves 4A. Analytical TLC was performed using glass-backed silica gel 60 (E. Merck). Microanalyses for C, H, and N were obtained using a Yanagimoto MT-3 apparatus.

General procedure for the preparation of 4-alkoxy-1,3-benzenedicarbonitriles (2):

A solution of 4-nitrobenzonitrile (1.0 equivalent) and KCN (1.5 equivalent) in dry DMSO (5 mL/mmol) was heated at 100 °C with stirring for 1 h. The mixture was cooled and K_2CO_3 (0.5 equivalent) and alkyl halide (2-4 equivalents) were introduced to the reaction mixture. Further stirring was continued for 1 to 24 h at rt to 80 °C until the reaction was accomplished. The reaction mixture was poured into water, and the products were extracted with AcOEt. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. Subsequent purification of the residue by silica gel column chromatography afforded 4-alkoky-1,3-benzenedicarbonitrile.

4-Ethoxy-1,3-benzenedicarbonitrile (2a):

colorless crystal; mp 155-156 °C (EtOH); ^{1}HNMR ($CDCl_3$): δ 1.53 (3 H, t, J = 7 Hz), 4.24 (2 H, q, J = 7 Hz), 7.05 (1 H, d, J = 9 Hz), 7,80 (1 H, dd, J = 9 and 2 Hz), 7.86 (1 H, d, J = 2 Hz); ^{13}CNMR($CDCl_3$): δ 14.30, 65.79, 103.74, 104.69, 113.03, 114.25, 117.09, 137.68, 138.08, 163.32; FT-IR (KBr): ν = 2930, 2232, 1507, 1304 cm^{-1}; HRMS: m/z Calcd for $C_{10}H_8N_2O$ 172.0637, Found 172.0667; Anal. Calcd for $C_{10}H_8N_2O$·1/4 EtOH: C, 68.7; H, 5.2; N, 15.3. Found: C, 68.7; N, 5.2; 14.9.

4-(2-Methylpropoxy)-1,3-benzenedicarbonitrile (2b):

yellow solid; mp 128—132 °C (EtOH); ^{1}HNMR ($CDCl_3$): δ 1.09 (6 H, d, J = 7 Hz), 2.21 (1 H, m), 3.91 (2 H, d, J = 6 Hz), 7.04 (1 H, d, J = 9 Hz), 7.79 (1 H, dd, J = 9 and 2 Hz), 7.85 (1 H, d, J = 2 Hz); ^{13}CNMR($CDCl_3$): δ 18.96, 28.07, 76.05, 103.72, 104.65, 113.15, 114.14, 117.11, 137.59, 138.06, 163.54; FT-IR (KBr): ν = 2963, 2234, 1611, 1503, 1304, 1007, 833 cm^{-1}; HRMS: m/z Calcd for $C_{12}H_{12}N_2O$ 200.0950, Found 200.0938; Anal. Calcd for

$C_{12}H_{12}N_2O$: C, 72.0; H, 6.0; N, 14.0. Found: C, 71.8; H, 6.0; N, 14.4

4-Octyloxy-1,3-benzenedicarbonitrile (2c):

white solid; mp 92 °C ~ (sublim. EtOH); ^{1}HNMR ($CDCl_3$): δ 0.89 (3 H, t-like, J = 7 Hz), 1.3-1.4 (8 H, br), 1.50 (2 H, br), 1.89 (2 H, m), 4.15 (2 H, t, J = 7 Hz), 7.05 (1 H, d, J = 9 Hz), 7.79 (1 H, dd, J = 9 and 2 Hz), 7.86 (1 H, d, J = 2 H); ^{13}CNMR($CDCl_3$): δ 14.04, 22.57, 25.68, 28.57, 29.08, 29.11, 31.70, 70.06, 103.68, 104.58, 113.01, 114.14, 117.05, 137.61, 137.99, 163.45; FT-IR (KBr): ν = 2992, 2234, 1607, 1505, 1287 cm^{-1}; HRMS: m/z Calcd for $C_{16}H_{20}N_2O$ 256.1576, Found 256.1570; Anal. Calcd for $C_{16}H_{20}N_2O$: C, 75.0; H, 7.9; N, 10.9. Found: C, 74.9; H, 7.7; N, 10.8.

4-(2-Ethoxyethoxy)-1,3-benzenedicarbonitrile (2d):

yellow solid; mp 94.0—95.5 °C (EtOH); ^{1}HNMR ($CDCl_3$): δ 1.22 (3 H, t, J = 7 Hz), 3.62 (2 H, q, J = 7 Hz), 3.87 (2 H, t, J = 5 Hz), 4.33 (2 H, t, J = 5 Hz), 7.14 (1 H, t, J = 5 Hz), 7.80 (1 H, dd, J = 9 and 2 Hz), 7.86 (1 H, d, J = 2 Hz); ^{13}CNMR($CDCl_3$): δ 15.08, 67.24, 68.29, 69.71, 103.88, 105.03, 113.57, 114.12, 116.96, 137.54, 137.90, 163.40; FT-IR (KBr): ν = 2895, 2232, 1607, 1505, 1286 cm^{-1}; HRMS: m/z Calcd for $C_{12}H_{12}N_2O_2$ 216.0899, Found 216.0859; Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.7; H, 5.6; N; 13.0. Found: C, 66.3; H, 5.6; N; 13.4.

4-Benzyloxy-1,3-benzenedicarbonitrile (2e):

yellow solid; mp 181—183 °C (MeOH); ^{1}HNMR (DMSO-d_6): δ 5.30 (2 H, s) 7.10 (1 H, d, J = 9 Hz), 7.36-7.43 (5 H, m), 7.77 (1 H, dd, J = 9 and 2 Hz), 7.88 (1 H, d, J = 2 Hz); ^{13}CNMR($CDCl_3$): δ 71.45, 104.13, 105.23, 113.80, 114.14, 116.93, 127.08, 128.80, 129.00, 134.25, 137.70, 137.99, 162.91; FT-IR (KBr): ν = 3057, 2236, 1611, 1508, 1306, 988 cm^{-1};. HRMS: m/z Calcd for $C_{15}H_{10}N_2O$ 234.0793, Found 234.0832; Anal. Calcd for $C_{15}H_{10}N_2O$: C, 76.9; H, 4.3; N; 12.0. Found: C, 76.9; H, 4.6; N, 12.1.

4-(2-Naphthylmethoxy)-1,3-benzenedicarbonitrile (2f):

yellow solid; mp 220—221 °C (MeOH); ^{1}HNMR ($CDCl_3$): δ 5.47 (2 H, s), 7.14 (1 H, d, J = 9 Hz), 7.50-7.55 (3 H, m), 7.75 (1 H, dd, J = 9 and 2 Hz), 7.83-7.91 (5 H, m); ^{13}CNMR($CDCl_3$): δ 71.40, 102.59, 104.33, 114.86, 115.01, 117.61, 125.68, 126.06, 126.72, 127.03, 127.90, 128.11, 128.65, 132.90, 132.99, 138.49, 139.23, 163.04; FT-IR (KBr): ν = 2235, 1610, 1507, 1306, 988, 808 cm^{-1};. HRMS: m/z Calcd for $C_{19}H_{12}N_2O$ 284.0950, Found 284.0991; Anal. Calcd for $C_{19}H_{12}N_2O$: C, 80.3; H, 4.3; N; 9.9. Found: C, 80.2; H, 4.4; N, 9.7.

4-(2-Methylpropoxy)-3-cyanobenzthioamide (6):

To a solution of HCl in DMF (6—7 N, 8 mL) was added **2b** (590 mg, 2.95 mmol) at rt. Thioacetamide (550 mg, 7.3 mmol) was added to the mixture, then it was heated at 45°C with stirring for 40 h. The products were extracted with AcOEt. The organic layer was washed with three portions of water to remove thioacetamide, dried over Na_2SO_4, and then evaporated. The residue was treated with $CHCl_3$ (20 mL) and the precipitate was removed by filtration. The filtrate was concentrated, and the resulting mixture was purified by silica gel column chromatography (hexane/AcOEt, 3:1) to give **6** (590 mg, 2.5 mmol, 85 %) as a dark yellow crystal (mp 123—124 °C): ^{1}HNMR ($CDCl_3$): δ 1.08 (6 H, d, J = 7 Hz), 2.20 (1 H, m), 3.90 (2 H, d, J = 7 Hz), 6.96 (1 H, d, J = 9 Hz), 8.11 (1 H, d, J = 2 Hz), 8.16 (1 H,

dd, J = 9 and 2 Hz); ^{13}CNMR($CDCl_3$): δ 19.03, 28.12, 75.85, 101.76, 111.91, 115.51, 131.35, 132.15, 134.32, 163.39, 199.10; FT-IR (KBr): ν 3165, 2232, 1642, 1601, 1503, 1302, 1005 cm^{-1}; HRMS: m/z Calcd for $C_{12}H_{14}N_2OS$ 234.0827, Found 234.0834; Anal. Calcd for $C_{12}H_{14}N_2OS$: C, 61.5; H, 6.0; N, 12.0. Found: C, 61.4; H, 6.0; N, 11.9.

4-Methyl-2-(4-(2-Methylpropoxy)-3-cyanophenyl)-5-thiazolecarboxylic acid (TEI-6720):

A solution of **6** (400 mg, 1.65 mmol) and ethyl 2-chloroacetoacetate (340 mg, 1.65 mmol) in ethanol (4 mL) was heated at 100 °C with stirring for 2 h. After cooling, the mixture was washed with brine, and the products were extracted with two portions of AcOEt. The combined organic layer was dried over Na_2SO_4, and evaporated. Purification by column chromatography (hexane/AcOEt, 3:1) on silica gel afforded ethyl 4-methyl-2-(4-(2-methylpropyloxy)-3-cyanophenyl)-5-thiazolecarboxylate (306 mg). It was hydrolyzed with 1N-NaOH solution (1.2 mL) in the mixture of THF (3 mL) and EtOH (3 mL) for 1 h at 60°C. The mixture was neutralized with 1N-HCl solution, and the formed crystal was collected by filtration. The sample was recrystallized from acetone to give TEI-6720 (183 mg, 5.8 mmol, 35 %) as a colorless crystal (mp 201—202 °C): ^{1}HNMR (DMSO-d_6): δ 1.04(6 H, d, J = 7 Hz), 2.12 (1 H, m, J = 7 Hz), 2.67 (3 H, s), 3.99 (2 H, d, J = 7 Hz), 7.34 (1 H, d, J = 9 Hz), 8.20 (1 H, dd, J = 9 and 2 Hz), 8.25 (1 H, d, J = 2 Hz); ^{13}CNMR($CDCl_3$): δ 17.68, 19.05, 28.18, 75.76, 103.04, 112.68, 115.31, 121.24, 125.71, 132.22, 132.74, 162.71, 162.98, 167.28, 168.60; FT-IR (KBr): ν = 2960, 2880, 2230, 1700, 1680, 1600, 1430, 1130 cm^{-1}; HRMS: m/z Calcd for $C_{16}H_{16}N_2O_3S$ 316.0882, Found 316.0861; Anal. Calcd for $C_{16}H_{16}N_2O_3S$: C, 60.7; H, 5.1; N, 8.9. Found: C, 60.7; H, 5.1; N, 8.9.

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