A Facile and Practical Synthesis of 9-Methyl-3-(1*H*-tetrazol-5-yl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one

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A facile and practical synthesis of 9-methyl-3-(1*H*-tetrazol-5-yl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (4), the potassium salt of which is used clinically as an anti-asthma agent, is described. Treatment of a key intermediate (6b), prepared from 2-amino-3-methylpyridine (1) and 2-ethoxymethylene-1,3-propanedinitrile, with sodium azide in *N,N*-dimethylformamide gave predominantly the cyanotetrazole (7a), while in acetic acid it gave exclusively the iminotetrazole (7b), which was easily converted into 4 by acid hydrolysis. A one-pot process starting from 6b to give 4, avoiding the use of explosive aluminum azide, was established.

Key words anti-asthma agent; 1*H*-tetrazole; 4*H*-pyrido[1,2-*a*]pyrimidine; sodium azide; alternative synthesis; one-pot synthesis

Some 5-(1*H*-tetrazol-5-yl)-4*H*-pyrimidin-4-one derivatives have been reported to inhibit release of chemical mediators from sensitized mast cells.1-3) Among them, 9-methyl-3-(1*H*-tetrazol-5-yl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**4**) is clinically used as its potassium salt4) for oral prophylactic treatment of asthma.

The synthesis of **4**, reported by Juby,3) involves reaction of ethyl 2-cyano-3-(3-methyl-2-pyridylamino)acrylate (**2**) or 3-cyano-9-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**3**) with aluminum azide as shown in Chart 1. Although the reaction is simple and involves a single step, it uses a highly explosive reagent, aluminum azide5) and the yield is rather low. Moreover, the preparation of **3** involves 4 steps from **1**. Considering these drawbacks, the method appeared to be impracticable for large-scale production of **4**.

In this paper, we describe an alternative facile synthesis of **4** that is suitable for large-scale production. Tracing Juby's procedure, we found that the reaction of **2** with aluminum azide gave 3-ethoxycarbonyl-4-imino-9-methyl-4*H*-pyrido[1,2-*a*]pyrimidine (**5**) as a by-product along with the desired compound (**4**). The by-product (**5**) is a cyclization compound of **2** between the nitrogen of the pyridine ring and the cyano group. We considered that the use of a *gem*-dicyano compound, 2-[(3-methyl-2-pyridylamino)methylene]propanedinitrile (**6a**), in place of **2** in this reaction would avoid the formation of **5**; the reaction is expected to give only 4-imino-9-methyl-3-(1*H*-tetrazol-5-yl)-4*H*-pyrido[1,2-*a*]pyrimidine (**7b**), which may be easily converted into **4** by acid hydrolysis (Chart 2).

Literature survey revealed6,7) that ring-chain tautomerism exists in condensation products (**6a** and **6b**) of 3-methyl-2-aminopyridine (**1**) and 2-ethoxymethylene-1,3-propane-dinitrile, and the ring tautomer, 3-cyano-4-imino-9-methyl-4*H*-pyrido[1,2-*a*]pyrimidine (**6b**), exists predominantly in solution.7) Therefore, we studied the reaction using the condensation products, assuming that **6b** is an equivalent of a *gem*-dicyano compound (**6a**) as a starting material. The results are summarized in Table 1.

Treatment of **6b** with 1 eq of aluminum azide gave exclusively the desired compound (**7b**) in 83% yield, as expected (entry 1). The structure was determined on the basis of spectral data; the IR spectrum confirmed the absence of the cyano group in **7b**, and the ^{1}H-NMR spectrum showed a singlet signal at 9.91 ppm assigned to the proton at the 2-position in the pyrido[1,2-*a*]pyrimidine ring.

We next attempted the reaction of **6b** with sodium azide or ammonium azide. Since the use of polar aprotic solvents such as *N,N*-dimethylformamide (DMF) was reported8) to facilitate tetrazole formation from a nitrile compound with sodium azide or ammonium azide, we carried out the reaction of **6b** with 1 eq of sodium or ammonium azide in DMF (entries 2 and 3). The conversion of the

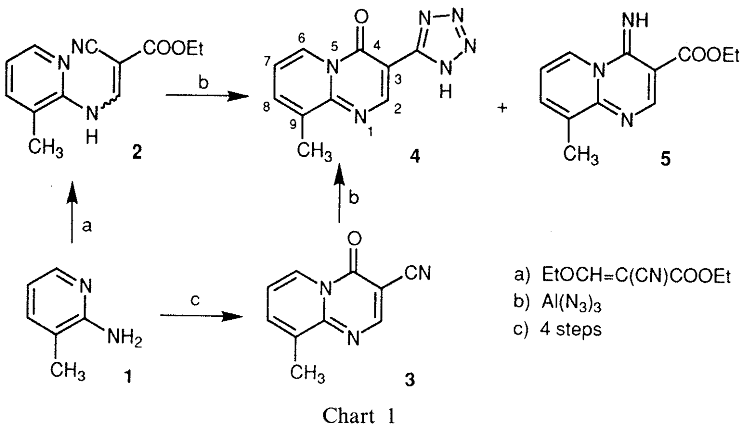

Chart 1

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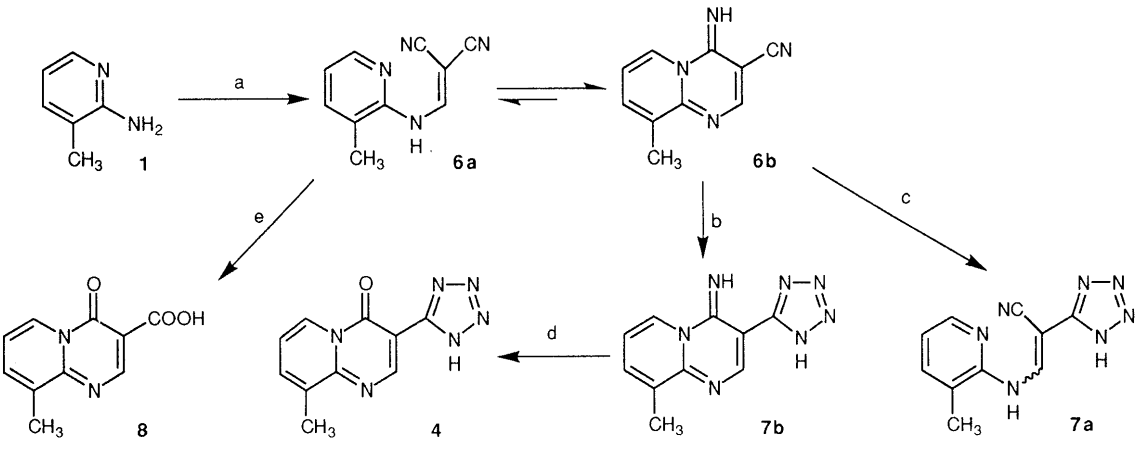

a) ref. 6 b) NaN$_3$, AcOH, refl., 1 h / quant. c) NaN$_3$, DMF, 95°C, 5 h / 74% d) 1 N HCl, refl., 1 h / 85% e) ref. 7

Chart 2

Table 1. Reaction of **6b** with Various Azides

Entry	Azide	Solvent	Conditions		Ratio of products[a]		Yield (%)[b]
			Temp. (°C)	Time (h)	**7a**	**7b**	
1	$Al(N_3)_3$	THF	Reflux	1	0	10	83
2	NaN_3	DMF	95	5	5	1	74
3	NH_4N_3	DMF	95	5	4	1	73
4	NaN_3	AcOH	115	1	0	10	Quantitative

a) Determined by ^{1}H-NMR. *b*) Combined yield of **7a** and **7b**.

nitrile (**6b**) into the tetrazole (**7b**) proceeded smoothly only at high temperature to give a mixture of 3-(3-methyl-2-pyridylamino)-2-(1*H*-tetrazol-5-yl)acrylonitrile (**7a**) and **7b**; the desired compound **7b** was the minor product.

The structure of **7a** was determined on the basis of ^{1}H-NMR and IR spectral data. In the IR spectrum, an absorption at 2220 cm^{-1} assigned to the cyano group was observed. In the ^{1}H-NMR spectrum, two doublet signals observed at 8.76 and 10.93 ppm, each with a coupling constant of 12.1 Hz, suggested the presence of =CH–NH– moiety in **7a**. Compounds **7a** and **7b** were easily distinguishable by different color generation on a TLC plate containing three fluorescent substances[9] under UV irradiation. In order to obtain **7b** exclusively from **6b**, we further studied the reaction of **6b** with sodium azide in various solvents. Interestingly, smooth conversion of **6b** into **7b** was observed when acetic acid was used as the solvent (entry 4); heating of a mixture of **6b** and sodium azide in acetic acid for 1 h afforded **7b** as a sole product in quantitative yield. The product was easily separated in high purity from the reaction mixture upon cooling to room temperature.

To our knowledge, no example of using acetic acid as a solvent in the conversion of a nitrile into a tetrazole compound has been reported.Conversion of a nitrile into a tetrazole in alcohol solution using equimolar sodium azide and acetic acid[10,11] proceeds through nascent hydrazoic acid, and generally requires high temperature, extended reaction time and the use of a sealed vessel.[8] It is noteworthy that the conversion of **6b** into **7b** in acetic acid solution proceeded smoothly and rather rapidly in an open vessel.

The iminotetrazole (**7b**) thus obtained was converted easily into the desired compound (**4**) by acid hydrolysis; a solution of **7b** in 1 N hydrochloric acid was heated for 1 h with stirring, and cooling the solution to room temperature gave analytically pure **4** in 85% yield merely by filtration from the reaction mixture.

A possible alternative synthesis of **4** from **6b** *via* **3** is ruled out, because acid hydrolysis of **6b** was reported[6,7] to give preferentially an acid derivative (**8**) instead of giving the keto compound (**3**). Thus, the synthesis of **4** was improved by using **6b** as a key intermediate in terms of the number of reaction steps and the overall yield from **1**.

We further tried to develop a one-pot synthesis of **4** from **6b** in order to make the whole procedure more convenient and simple. After scrutiny of various reaction conditions, a one-pot synthesis of **4** was accomplished; a mixture of **6b** with sodium azide in acetic acid was heated for 1 h, then aqueous hydrochloric acid was added to the reaction mixture and subsequent heating for 2 h gave the desired product (**4**) in 89% yield merely by filtration from the reaction mixture. The product (**4**) thus obtained was found to be over 99.5% pure by HPLC analysis.

In summary, we have developed a new practical synthesis of **4** from **6b**. The reaction of **6b** with sodium azide in acetic acid proceeded through the iminotetrazole (**7b**), and subsequent hydrolysis of **7b** gave the desired product (**4**), which was isolated in analytically pure form merely by filtration from the reaction mixture. The one-pot process involving these two reactions is convenient and practical for large-scale production of **4** in that the use of explosive aluminum azide can be avoided.

Experimental

All melting points were determined on a Mettler apparatus, type FP-61, and are uncorrected. IR spectra were recorded on JASCO IRA-2 spectrophotometer using KBr disks. ^{1}H-NMR spectra were recorded on a JEOL GSX 270 spectrometer with tetramethylsilane as an internal standard. Mass spectra were recorded in the EI mode on a Shimadzu

GCQP-1000 spectrometer. Silicagel 70FM Plate-wako was used for TLC tests, and Wakogel C-200 for silica gel column chromatgraphy. All reagents and solvents were of commercial quality.

Isolation of By-product, 3-Ethoxycarbonyl-4-imino-9-methyl-4*H*-pyrido[1,2-*a*]pyrimidine (5) The reaction of ethyl 2-cyano-3-(3-methyl-2-pyridylamino)acrylate (**2**) (5.0 g, 21.6 mmol) with $AlCl_3$ (3.51 g, 26.3 mmol) and NaN_3 (5.13 g, 78.9 mmol) was run according to the procedure of Juby.[3] After removal of **4** (2.36 g, 47.9%) by filtration, the filtrate was extracted twice with $CHCl_3$ (100 ml). The combined extracts were washed with saturated $NaHCO_3$ (20 ml) and brine (20 ml), dried with $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo*, and the residue was recrystallized twice from CH_3CN to give 1.2 g (24.0%) of **5**, mp 96—99 °C. IR (KBr) cm^{-1}: 3300 (>NH), 1695 (>C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, t, J=6.96 Hz, $CH_2C\underline{H}_3$), 2.54 (3H, s, CH_3), 4.36 (2H, q, J=6.96 Hz, $C\underline{H}_2CH_3$), 7.04 (1H, dd, J=6.96, 6.96 Hz ,C^7-H), 7.66 (1H, dd, J=1.83, 6.96 Hz, C^8-H), 8.63 (1H, s, C^2-H), 9.35 (1H, br s, NH), 9.43 (1H, dd, J=1.83, 6.96 Hz, C^6-H). *Anal.* Calcd for $C_{12}H_{13}N_3O_2$: C, 62.33 ; H, 5.67 ; N, 18.17. Found: C, 62.37; H, 5.60; N, 18.22.

Preparation of 3-Cyano-4-imino-9-methyl-4*H*-pyrido[1,2-*a*]pyrimidine (6b) The title compound (**6b**) was prepared from 2-amino-3-methylpyridine (**1**) (160 g, 1.48 mol) and 2-ethoxymethylene-1,3-propanedinitrile (150 g, 1.23 mol) according to the procedure of Okamoto *et al.*[6] to give 207 g (91.4%) of **6b**, mp 165—167 °C (lit.,[7] mp 164—166 °C). IR (KBr) cm^{-1}: 3400 (>NH), 2200 (–C≡N). ^{1}H-NMR ($CDCl_3$) δ: 2.54 (3H, s, CH_3), 7.13 (1H, dd, J=6.96, 6.96 Hz, C^7-H), 7.42 (1H, br s, NH), 7.74 (1H, dd, J=1.47, 6.96 Hz, C^8-H), 8.10 (1H, s, C^2-H), 9.28 (1H, dd, J=1.47, 6.96 Hz, C^6-H).

Reaction of 6b with Aluminum Azide A mixture of $AlCl_3$ (1.74 g, 13.0 mol), NaN_3 (2.55 g 39.2 mmol) and **6b** (2.0 g, 10.9 mmol) in tetrahydrofuran (THF) (24 ml) was refluxed with stirring for 1 h, then cooled to room temperature. The mixture was poured into H_2O (150 ml) and acidified with concentrated HCl (10 ml) to pH 1. The resulting precipitates were collected by filtration, washed successively with H_2O (20 ml) and MeOH (20 ml), and air-dried to give 2.05 g (83.1%) of 4-imino-9-methyl-3-(1*H*-tetrazol-5-yl)-4*H*-pyrido[1,2-*a*]pyrimidine (**7b**), mp 233 °C (dec.). IR (KBr): 3400 (>NH) cm^{-1}. ^{1}H-NMR (CF_3COOD) δ: 2.97 (3H, s, CH_3), 7.97 (1H, dd, J=7.32, 7.32 Hz, C^7-H), 8.40 (1H, dd, J=1.28, 7.32 Hz, C^8-H), 9.03 (1H, dd, J=1.28, 7.32 Hz, C^6-H), 9.91 (1H, s, C^2-H). MS m/z: 227 (M^+). *Anal.* Calcd for $C_{10}H_9N_7 \cdot H_2O$: C, 48.98; H, 4.52; N, 39.98. Found: C, 48.95; H, 4.48; N, 40.07.

Reaction of 6b with Sodium Azide in DMF A mixture of **6b** (2.0 g, 10.9 mmol) and NaN_3 (0.78 g, 11.9 mmol) in DMF (20 ml) was stirred at 90—95 °C for 5 h and cooled to room temperature. The mixture was poured into H_2O (150 ml) and acidified with concentrated HCl (10 ml) to pH 1, and the resulting precipitates were collected by filtration. The solid was washed with H_2O (20 ml) and then with MeOH (20 ml), and air-dried to give 1.82 g (73.8%) of a mixture of **7a** and **7b**. The product ratio of **7a** and **7b** was determined on the basis of the integration ratio of methyl protons (δ 2.41 ppm for **7a** and δ 2.94 ppm for **7b**) at the 9-position of the pyrido[1,2-*a*]pyrimidine ring in the ^{1}H-NMR spectrum (Table 1). TLC [solvent, $CHCl_3$–MeOH–NH_4OH (100 : 10 : 1, v/v)]; the spots of **7a** and **7b** appeared dark green and light yellow, respectively. Isolation of **7a** was carried out by column chromatography using silica gel [eluent, $CHCl_3$–MeOH–NH_4OH (900 : 100 : 1, v/v)] to give 1.4 g (56.7%) of 3-(3-methyl-2-pyridylamino)-2-(1*H*-tetrazol-5-yl)acrylonitrile (**7a**), mp 191 °C (dec.). IR (KBr) cm^{-1}: 3050 (>NH), 2220 (–C≡N). ^{1}H-NMR (DMSO-d_6) δ: 2.41 (3H, s, CH_3), 7.11 (1H, dd, J=4.76, 7.32 Hz, C^5-H), 7.73 (1H, dd, J=1.46, 7.32 Hz, C^4-H), 8.22 (1H, dd, J=1.46, 4.76 Hz, C^6-H), 8.76 (1H, d, J=12.09 Hz, >NH–C$\underline{H}$=C<), 10.93 (1H, d, J=12.09 Hz, >N$\underline{H}$–CH=C<), 13.18 (1H, br s, tetrazole-NH). MS m/z: 227 (M^+). *Anal.* Calcd for $C_{10}H_9N_7 \cdot H_2O$: C, 48.98; H, 4.52; N, 39.98. Found: C, 48.62; H, 4.53; N, 40.18.

Reaction of 6b with Ammonium Azide in DMF A mixture of **6b** (2.0 g, 10.9 mmol), NH_4Cl (0.64 g, 11.9 mmol) and NaN_3 (0.78 g, 11.9 mmol) in DMF (20 ml) was stirred at 90—95 °C for 5 h. After worked up as described above, a mixture of **7a** and **7b** was obtained (1.80 g, 73.0%). The product ratio of **7a** and **7b** is shown in Table 1.

Reaction of 6b with Sodium Azide in Acetic Acid A mixture of **6b** (20 g, 109 mmol) and NaN_3 (7.1 g, 109 mmol) in AcOH (20 ml) was heated with stirring at 110—115 °C for 1 h. The reaction progress was monitored by checking the spots of **6b** and **7a** by TLC [$CHCl_3$–MeOH–NH_4OH (100 : 10 : 1, v/v)]. The mixture was cooled to room temperature and poured into H_2O (120 ml) to yield a yellow solid, which was collected by filtration, washed with H_2O (20 ml) and air-dried to give 24.8 g (quantitative) of **7b**. Spectral analysis showed that the product was free from **7a**.

Preparation of 4 from 7b A mixture of **7b** (2.0 g, 10.9 mmol) in 1 N HCl (20 ml) was heated with stirring at 95—100 °C for 1 h, then cooled to room temperature. The resulting precipitates were collected by filtration, washed with H_2O (20 ml) and air-dried to give 1.7 g (84.6%) of **4**. All analytical data were identical with those of an authentic sample prepared by the procedure of Juby.[3]

Preparation of 4 from 6b by One-Pot Procedure A mixture of **6b** (195 g, 1.06 mol) and NaN_3 (69 g, 1.06 mol) in AcOH (780 ml) was heated with stirring at 110—115 °C for 1 h. The reaction progress was monitored by TLC as described above. Then, concentrated HCl (236 g) and H_2O (540 ml) were added to the mixture and the whole was further heated with stirring at 100—110 °C for 2 h. It was cooled to room temperature, and the precipitates were collected by filtration, washed with H_2O (100 ml) and air-dried at room temperature to yield 215 g (88.9%) of **4**. The purity of the product was over 99.5% as determined by HPLC analysis.[12]

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12) Conditions of HPLC analysis: column, Wakosil 5C18 (4.6 × 150 mm); eluent, CH_3CN–H_2O–0.5 N tetrabutylammonium hydroxide (80 : 20 : 1, v/v), adjusted to pH 6.4 with phosphoric acid.