A FACILE AND CONVENIENT SYNTHESIS OF 9-METHYL-3-(1*H*-TETRAZOL-5-YL)-4*H*-PYRIDO[1,2-*a*]PYRIMIDIN-4-ONE POTASSIUM

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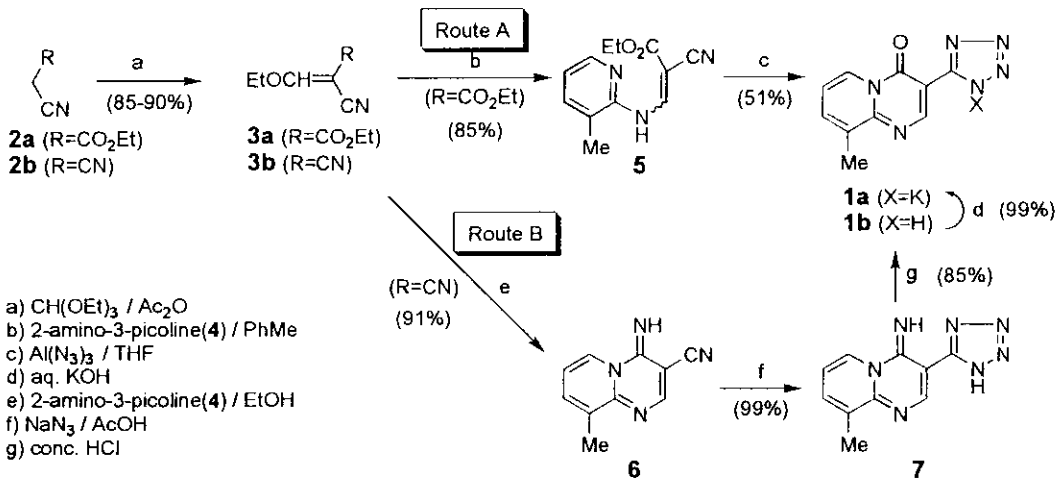
Abstract — Two convenient synthetic methods of anti-allergy agent, 9-methyl-3-(1*H*-tetrazol-5-yl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one potassium (**1a**), are described. Heating of a mixture of malononitrile (**2b**), 2-amino-3-picoline (**4**), ethyl orthoformate, and sodium azide in acetic acid, followed by hydrolysis with hydrochloric acid gave 9-methyl-3-(1*H*-tetrazol-5-yl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**1b**) which was led to **1a** by treatment with potassium hydroxide. The use of ethyl cyanoacetate (**2a**) instead of **2b** afforded ethyl 3-(3-methyl-2-pyridylamino)-2-(1*H*-tetrazol-5-yl)acrylate (**8**) which was also led to **1a** by treatment with potassium hydroxide.

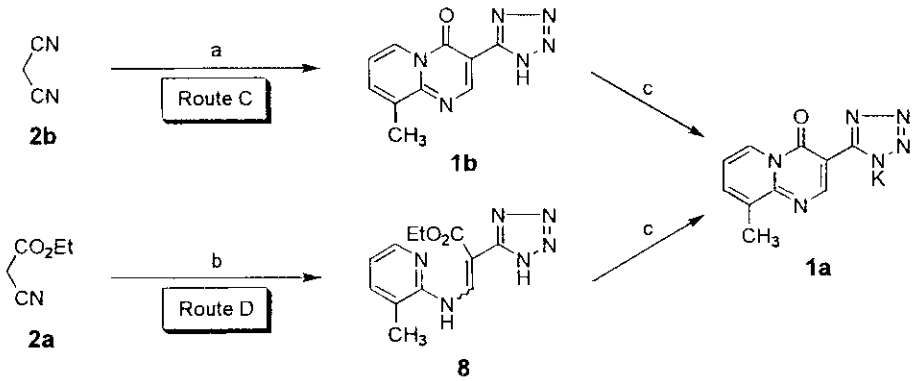
9-Methyl-3-(1*H*-tetrazol-5-yl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one potassium (**1a**),[1] anti-allergy agent, has been clinically used for the treatment of asthma.[2] The synthesis of **1a** starting from ethyl cyanoacetate (**2a**) *via* ethyl 2-cyano-3-(3-methyl-2-pyridylamino)acrylate (**5**) was reported by Juby (Route A in Scheme 1).[3] It involved the formation of a tetrazole ring using a hazardous reagent, aluminum azide[4] and its yield is low.



Scheme 1

Recently, we developed an alternative synthesis of **1a** starting from malononitrile (**2b**) *via* 3-cyano-4-imino-9-methyl-4*H*-pyrido[1,2-*a*]pyrimidine (**6**) (Route B in Scheme 1).[5] In this synthesis, **6** was converted in acetic acid into **7** in good yield by the treatment of sodium azide, which was safer to handle than aluminum azide. However, this method required multi-step to afford **1a** from a commercially available material (**2b**) and handling of a strong sensitizing agent (**3b**).

In this note, we wish to describe two kinds of a facile and convenient preparation of **1a** using a one-pot synthesis of **1b** or **8** (Scheme 2).



a) i) 2-amino-3-picoline(**4**), $CH(OEt)_3$, NaN_3 / AcOH, ii) conc. HCl
b) 2-amino-3-picoline(**4**), $CH(OEt)_3$, NaN_3 / AcOH
c) 2*N* KOH / IPA

Scheme 2

It was reported that the pyrido[1,2-*a*]pyrimidine skeleton of **1a** was prepared by condensation of **2b**, 2-amino-3-picoline (**4**), and ethyl orthoformate.[6] In addition, we found that acetic acid was an efficient solvent for conversion of a cyano group into a 1*H*-tetrazole ring with sodium azide.[4] Therefore, the condensation reaction in acetic acid containing sodium azide was expected to attain both pyrido[1,2-*a*]pyrimidine and 1*H*-tetrazole ring closures.

First, we investigated a reaction of **2b** and **4** with ethyl orthoformate in acetic acid containing sodium azide (Route C in Scheme 2). Heating of a mixture of **2b**, **4**, ethyl orthoformate and sodium azide in acetic acid, followed by hydrolysis with hydrochloric acid gave 9-methyl-3-(1*H*-tetrazol-5-yl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**1b**) in 68% yield. The yield was not influenced by a way of blend of the reagents. The structure of **1b** was confirmed by direct comparison with an authentic sample.[3] Treatment of **1b** with aqueous potassium hydroxide afforded **1a** in quantitative yield.

When this condensation reaction was carried out in other acidic solvents, such as formic acid or trifluoroacetic acid, many unidentified by-products were produced. Thus, the pH of the reaction mixture was seemed to be one of the critical factors both for conversion of a cyano group into 1*H*-tetrazole ring and the condensation of **2a** and **4** with ethyl orthoformate.

Next, we tried to use **2a** in place of **2b** (Route D in Scheme 2). Condensation of a mixture of **2a**, **4**, ethyl

orthoformate and sodium azide in acetic acid afforded ethyl 3-(3-methyl-2-pyridylamino)-2-(1*H*-tetrazol-5-yl)-acrylate (**8**) as crystalline powder in 62% yield.

The structure of **8** was determined on the basis of IR and ^{1}H-NMR spectral data. The IR spectrum indicated the absence of cyano group. The ^{1}H-NMR spectrum showed a doublet signal at 4.35 ppm and a triplet signal at 1.35 ppm. These signals were assigned to the protons of an ethyl group. Moreover, two doublet signals observed at 11.44 and 9.23 ppm with a coupling constant of 13.5 Hz suggested the presence of a =CH-NH- moiety.

Treatment of **8** with aqueous potassium hydroxide afforded **1a** in 95% yield while attempts of cyclization of **8** under aqueous acidic conditions, such as aqueous hydrochloric acid or sulfuric acid, were unsuccessful.

In summary, we accomplished two convenient methods for the synthesis of **1a** employing a one-pot synthesis of **1b** or **8**. These methods were able to provide **1a** in only two steps starting from **2**.

EXPERIMENTAL

All melting points are determined on a Yanagimoto apparatus and are uncorrected. IR spectra were recorded on a 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. All reagents and solvents were of commercial quality.

9-Methyl-3-(1*H*-tetrazol-5-yl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (1b) (from 2b)

A mixture of malononitrile (**2b**) (3.3 g, 50 mmol), 2-amino-3-picoline (**4**) (5.4 g, 50 mmol), ethyl orthoformate (8.2 g, 55 mmol) and sodium azide (3.6 g, 55 mmol) in acetic acid (50 mL) was heated at 90°C for 2 h. Concentrated hydrochloric acid (25 mL) was poured into the mixture, which was further heated at 90°C for 2 h. The mixture was cooled and diluted with water (50 mL). The resulting precipitates were collected in suction and dried to give **1b** (7.7 g, 67.5 %), mp 306°C(dec.) (lit.,[3] 310-311°C(dec.)). All spectral data of **1b** were identical with those of an authentic sample.[3] IR (KBr): 3100, 1670, 1595, 1480, 1330, 1080, 900, 780 cm^{-1}. ^{1}H-NMR (DMSO-*d*6):2.63 (3H, s, C<u>H</u>3), 7.54 (1H, t, *J*=7.0 Hz, C7-H), 8.09 (1H, d, *J*=7.0 Hz, C8-H), 9.15 (1H, d, *J*=7.0 Hz, C6-H), 9.24 (1H, s, C2-H).

9-Methyl-3-(1*H*-tetrazol-5-yl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one potassium (1a) (from 1b)

A suspension of **1b** (4.6 g, 20 mmol), 2*N* potassium hydroxide (15 mL) in 2-propanol (20 mL) was heated at 50°C for 1 h. The mixture was cooled and diluted with 2-propanol (40 mL). The resulting precipitates were collected in suction filtration and dried to give **1a** (5.3 g, 99 %) as pale yellow crystalline powder. mp 317°C (dec.). All spectral data of **1a** were identical with those of an authentic sample.[3] IR (KBr): 1690, 1495, 1450, 1310, 1160, 1140, 770 cm^{-1}. ^{1}H-NMR (D_2O): 2.15 (3H, s, C<u>H</u>3), 6.97(1H, t, *J*=7.0 Hz, C7-H), 7.38(1H, d, *J*=7.0 Hz, C8-H), 8.29 (1H, s, C2-H), 8.64(1H, d, *J*=7.0 Hz, C6-H).

Ethyl 3-(3-methyl-2-pyridylamino)-2-(1*H*-tetrazol-5-yl)acrylate (8)

A mixture of ethyl cyanoacetate (**2a**) (5.7 g, 50 mmol), **4** (5.4 g, 50 mmol), ethyl orthoformate (8.2 g, 55 mmol) and sodium azide (3.6 g, 55 mmol) in acetic acid (50 mL) was heated at 90°C for 2 h. After the mixture was

cooled and diluted with water (50 mL), the resulting precipitates were collected in suction filtration and dried to give **8** (8.4 g, 61 %) as pale yellow leaflets. mp 206-210℃. IR (KBr): 3150, 1660, 1620, 1580, 1460, 1400, 1240, 1100, 770 cm^{-1}. ^{1}H-NMR (DMSO-*d*6): 1.35 (3H, t, *J*=8.1 Hz, CH_2CH_3), 2.42 (3H, s, CH_3), 4.35 (2H, q, *J*=8.1 Hz, CH_2CH_3), 7.12 (1H, dd, *J*=8.1 and 5.4 Hz, Ar-H(C5)), 7.73 (1H, d, *J*=8.1 Hz, Ar-H(C4)), 8.26 (1H, d, *J*=5.4 Hz, Ar-H(C6)), 9.23 (1H, d, *J*=13.5 Hz, NHCH=C), 11.44 (1H, d, *J*=13.5 Hz, NHCH=C), 14.32 (1H, s, tetrazole-H). *Anal.* Calcd for $C_{12}H_{14}N_6O_2$: C, 52.55; H, 5.14; N, 30.64. Found: C, 52.47; H, 4.98; N, 30.42.

9-Methyl-3-(1*H*-tetrazol-5-yl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one potassium (1a) (from 8)

A suspension of **8** (5.5 g, 20 mmol), 2*N* potassium hydroxide (15 mL) and 2-propanol (20 mL) was refluxed for 2 h. The mixture was cooled and diluted with 2-propanol (20 mL). The resulting precipitates were collected in suction filtration and dried to give **1a** (5.2 g, 95 %) as pale yellow crystalline powder. All spectral data of **1a** were identical with those of an authentic sample as above.

REFERENCES AND NOTES

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