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SYNTHESIS OF 1-AMINO-1-ARYL-1,2-DIHYDROPYRROLO[3,4-*c*]-PYRIDIN-3-ONE DERIVATIVES BY THE REACTION OF 4-LITHIOPYRIDINE-3-CARBONITRILE WITH AROMATIC TERTIARY AMIDES

Kazuhiro Kobayashi,* Kazuhiro Nakagawa, and Taketoshi Kozuki

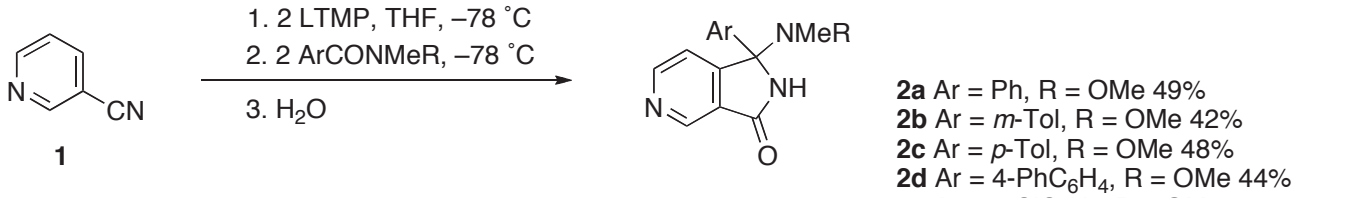
Division of Applied Chemistry, Department of Chemistry and Biotechnology, Graduate School of Engineering, Tottori University, 4-101 Koyama-minami, Tottori 680-8552, Japan; E-mail: kkoba@chem.tottori-u.ac.jp

Abstract – A one-pot procedure for the preparation of 1-amino-1-aryl-1,2-dihydropyrrolo[3,4-*c*]pyridin-3-one derivatives from pyridine-3-carbonitrile and aromatic tertiary amides has been developed. Thus, the reaction of 4-lithiopyridine-3-carbonitrile, generated by the treatment of pyridine-3-carbonitrile with lithium 2,2,6,6-tetramethylpiperidide (LTMP), with aromatic tertiary amides in THF at –78 ˚C yields the pyrrolopyridinone derivatives in moderate yields.

In the course of our study on the development of new methods for the preparation of heterocyclic compounds, we became in need of 2-aroylpyridine-3-carbonitriles. So we attempted the reaction of 4-lithiopyridine-3-carbonitrile[1] with *N*-methoxy-*N*-methylbenzamide. However, we were surprised to find that this reaction resulted in the formation of 1-methoxy(methyl)amino-1-phenyl-1,2-dihydropyrrolo-[3,4-*c*]pyridin-3-one. Herein, we wish to report the results of our study on the reaction of lithiopyridinecarbonitriles with aromatic tertiary amides, which offer a simple synthetic method for 1-amino-1-aryl-1,2-dihydropyrrolo[3,4-*c*]pyridin-3-one derivatives. The 1,2-dihydropyrrolo[3,4-*c*]-pyridine-3-one structure has been reported to be involved in the naturally occurring isoniazid–NAD(P) adducts.[2] 1,2-Dihydropyrrolo[3,4-*c*]pyridine-3-one derivatives have been mainly prepared by the reduction of pyrrolo[3,4-*c*]pyridine-1,3-diones.[2,3] Recently, a method based on microwave-assisted intramolecular hetero-Diels-Alder cycloaddition of acetylenic pyrimidines has been reported.[4] However, there have been no reports on the synthesis of this heterocyclic derivatives carrying an amino group at the 1-position.

First, the reaction of 4-lithiopyridine-3-carbonitrile with *N*-methoxy-*N*-methylbenzamide was examined under conditions illustrated in Scheme 1. Thus, the 4-position of pyridine-3-carbonitrile (**1**) was lithiated

with 2 equivalents of lithium 2,2,6,6-tetramethylpiperidide (LTMP) in THF at –78 ˚C under Laurt's conditions,[2] and the resulting lithium product was allowed to react with two equivalents of *N*-methoxy-*N*-methylbenzamide at the same temperature for 30 min. Aqueous workup was followed by purification of the crude product by column chromatography on silica gel to give 1-methoxy(methyl)amino-1-aryl-1,2-dihydropyrrolo[3,4-*c*]pyridin-3-one (**2a**) in 49% yield as the only structurally defined isolated product. 4-Benzoylpyridine-3-carbonitrile was not obtained at all. The use of one equivalent of the amide gave a rather poorer yield (21%), and the use of three equivalents did not improve the yield. Determination of the structure of **2a** was achieved on the basis of its spectral data. Mass spectrometry and elemental analysis established the molecular formula of the product to be $C_{15}H_{15}N_3O_2$. The IR spectrum showed absorption bands at 3187 and 1697 cm^{-1} due to N-H and C=O groups, respectively. The ^{13}C NMR spectrum exhibited thirteen signals including a signal at 169.25 assignable to the amide carbonyl carbon. The ^1H NMR spectral data are in good agreement with the structure of **2a** (see Experimental section).

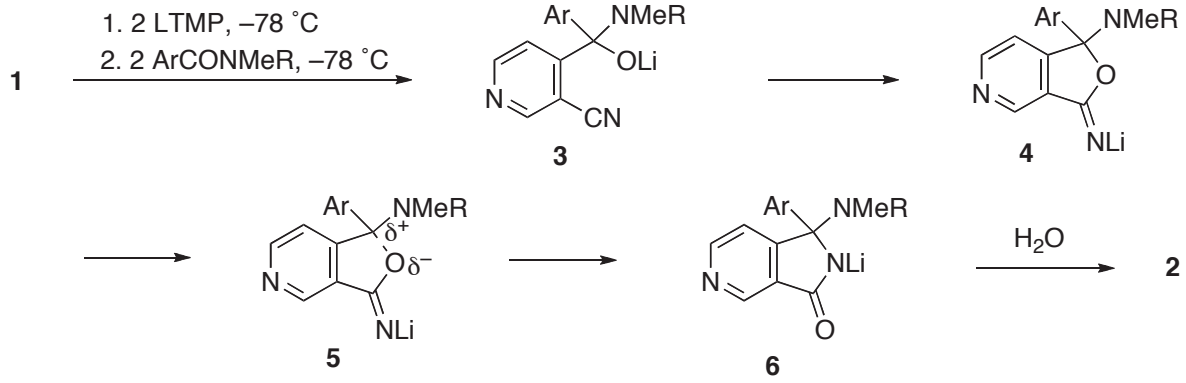


2a Ar = Ph, R = OMe 49%
2b Ar = *m*-Tol, R = OMe 42%
2c Ar = *p*-Tol, R = OMe 48%
2d Ar = 4-PhC_6H_4, R = OMe 44%
2e Ar = 3-ClC_6H_4, R = OMe 42%
2f Ar = 4-ClC_6H_4, R = OMe 42%
2g Ar = naphthalen-2-yl, R = OMe 40%
2h Ar = Ph, R = Me 31%
2i Ar = 3-ClC_6H_4, R = Me 28%
2j Ar = 3-$MeOC_6H_4$, R = Me 31%

Scheme 1

Encouraged by this result, the lithium product generated from **1** was then allowed to react with various tertiary amides. Using other nine aromatic tertiary amides, the corresponding 1-amino-1-aryl-1,2-dihydropyrrolo[3,4-*c*]pyridin-3-one derivatives (**2**) were obtained in moderate yields, as summarized in Scheme 1 as well. The results indicate that the yields of 1-methoxy(methyl)amino derivatives (**2a-g**) are somewhat higher than those of 1-dimethylamino derivatives (**2h-j**). This result may indicate that the methoxy group facilitates the rearrangement of **4** to **6** by stabilizing the transition state **5** shown below.

The formation of the products (**2**) from **1** and amides is thought to proceed as depicted in Scheme 2. The first step involves the addition of 3-cyanopyridin-4-yl anion to the carbonyl of the amides providing lithium alkoxide intermediate (**3**). Subsequent intramolecular addition of the alkoxide to the cyano function gave the lithioiminoether intermediate (**4**), of which rearrangement followed by protonation gives rise to **2**. Similar iminoether rearrangement reactions have been reported previously;[5] recently we have described the formation of 3-methyleneisoindolin-1-ones from the reaction of 2-formylbenzonitriles with dimethyloxosulfonium methylide via the corresponding imino anion intermediates.[5c]



Scheme 2

When **1** was lithiated with two equivalents of LDA and treated with two equivalents of *N*-methoxy-*N*-methylbenzamide under the same conditions described above, the yields of the desired product (**4a**) decreased to 32%. The reaction of the lithium product, generated from **1** and LTMP under the same conditions, with *N*-methoxy-*N*-methylpropanamide led to the formation of an intractable mixture of products. The use of 1-benzoylpyrrolidine gave also a similar result. It should be noted that the uses of pyridine-2-carbonitrile and pyridine-4-carbonitrile in place of pyridine-3-carbonitrile resulted in the formation of complex reaction mixtures of products, from which no trace amounts of the corresponding pyrrolopyridinone derivatives were obtained.

In conclusion, we have shown that a range of 1-amino-1-aryl-1,2-dihydropyrrolo[3,4-*c*]pyridin-3-one derivatives can be prepared through the lithiation of pyridine-3-carbonitrile with LTMP followed by treatment with aromatic tertiary amides. The present procedure should be efficient and valuable in organic synthesis, because this type of 1,2-dihydro-3*H*-pyrrolo[3,4-*c*]pyridine-3-one derivatives are difficult to obtain by using previous reactions.

EXPERIMENTAL

The melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were recorded with a Shimadzu FTIR-8300 spectrophotometer. The ^{1}H NMR spectra were recorded using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 MHz or JEOL LA400FT NMR spectrometer operating at 400 MHz. The ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 125 MHz or JEOL LA400FT NMR spectrometer operating at 100 MHz. Low-resolution MS spectra (EI, 70 eV) were measured by a JEOL JMS AX505 HA spectrometer. TLC was carried out on a Merck Kieselgel 60 PF_{254}. Column chromatography was performed using WAKO GEL C-200E. All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use.

Starting Materials. *N*-Methoxy-*N*-methylbenzamides were prepared from the respective benzoyl chlorides and *N*,*O*-dimethylhydroxylamine hydrochloride by the standard method. *n*-BuLi was supplied by Asia Lithium Corporation. All other chemicals used in this study were commercially available.

Typical Procedure for the Preparation of 1,2-Dihydropyrrolo[3,4-*c*]pyridin-3-ones (2). 1-Methoxy(methyl)amino-1-phenyl-1,2-dihydropyrrolo[3,4-*c*]pyridin-3-one (2a). To a stirred solution of LTMP (2.0 mmol), generated from 2,2,6,6-tetramethylpiperidine and *n*-BuLi by the standard method, in THF (4 mL) at –78 ˚C was added a solution of **1** (0.10 g, 1.0 mmol) in THF (2 mL) dropwise. After 30 min, a solution of *N*-methoxy-*N*-methylbenzamide (0.35 g, 2.1 mmol) in THF (1 mL) was added and stirring was continued for an additional 30 min at the same temperature before saturated aqueous NH_4Cl (15 mL) was added. The mixture was warmed to rt and the organic materials were extracted with AcOEt (3 × 10 mL). The combined extracts were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by preparative TLC on silica gel to give **2a** (0.13 g, 49 %); a white solid; mp 157–158 ˚C (hexane–CH_2Cl_2); IR (KBr) 3187, 1697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 3.36 (s, 3H), 7.38–7.42 (m, 5H), 7.75–7.77 (m, 2H), 8.72 (d, *J* = 4.9 Hz, 1H), 9.04 (s, 1H); ^{13}C NMR (100 MHz) δ 37.16, 60.30, 85.89, 117.91, 124.93, 125.74, 126.01, 128.91, 128.95, 140.95, 146.13, 152.63, 169.25; MS *m*/*z* 269 (M^+, 0.37), 209 (100). Anal. Calcd for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.60. Found: C, 66.79; H, 5.55; N, 15.52.

1-Methoxy(methyl)amino-1-(3-methylphenyl)-1,2-dihydropyrrolo[3,4-*c*]pyridin-3-one (2b): a white solid; mp 168–170 ˚C (hexane–CH_2Cl_2); IR (KBr) 3185, 1694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3H), 2.42 (s, 3H), 3.36 (s, 3H), 6.85 (br s, 1H), 7.16 (d, *J* = 7.8 Hz, 1H), 7.29 (t, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 5.4 Hz, 1H), 7.50 (s, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 8.71 (d, *J* = 5.4 Hz, 1H), 9.04 (s, 1H); ^{13}C NMR (100 MHz) δ 21.55, 39.32, 60.29, 85.75, 117.93, 122.90, 123.54, 124.80, 125.82, 126.15, 128.85, 129.73, 138.74, 146.14, 152.70, 169.10; MS *m*/*z* 283 (M^+, 0.46), 223 (100). Anal. Calcd for $C_{16}H_{17}N_3O_2$: C, 67.83; H, 6.05; N, 14.83. Found: C, 67.64; H, 6.14; N, 14.65.

1-Methoxy(methyl)amino-1-(4-methylphenyl)-1,2-dihydropyrrolo[3,4-*c*]pyridin-3-one (2c): a white solid; mp 70–72 ˚C (hexane–Et_2O); IR (KBr) 3206, 1705 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.34 (s, 3H), 2.42 (s, 3H), 3.36 (s, 3H), 7.01 (br s, 1H), 7.19 (d, *J* = 7.8 Hz, 2H), 7.41 (d, *J* = 5.0 Hz, 1H), 7.62 (d, *J* = 7.8 Hz, 2H), 8.71 (d, *J* = 5.0 Hz, 1H), 9.03 (s, 1H); ^{13}C NMR (125 MHz) δ 21.01, 37.11, 60.30, 85.73, 117.85, 125.63, 125.93, 126.78, 129.16, 129.62, 138.91, 146.13, 152.63, 169.07; MS *m*/*z* 283 (M^+, 0.42), 223 (100). Anal. Calcd for $C_{16}H_{17}N_3O_2$: C, 67.83; H, 6.05; N, 14.83. Found: C, 67.73; H, 6.04; N, 14.73.

1-(Biphenyl-4-yl)-1-methoxy(methyl)amino-1,2-dihydropyrrolo[3,4-*c*]pyridin-3-one (2d): a pale-yellow solid; mp 167–169 ˚C (hexane–CH_2Cl_2); IR (KBr) 3233, 1705 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.46 (s, 3H), 3.40 (s, 3H), 7.11 (br s, 1H), 7.36 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.4, 7.4 Hz, 2H), 7.46 (d, *J* = 5.2 Hz, 1H), 7.57 (d, *J* = 7.4 Hz, 2H), 7.65 (d, *J* = 8.1 Hz, 2H), 7.82 (d, *J* = 8.1 Hz, 2H), 8.74 (d, *J* = 5.2 Hz, 1H), 9.06 (s, 1H); ^{13}C NMR (125 MHz) δ 37.20, 60.36, 85.73, 117.93, 125.90, 126.20,

127.04 (2C), 127.62, 127.66, 128.83, 137.76, 140.08, 141.91, 146.26, 152.77, 169.08; MS *m/z* 345 (M^+, 0.21), 285 (100). Anal. Calcd for $C_{21}H_{19}N_3O_2$: C, 73.03; H, 5.54; N, 12.17. Found: C, 72.86; H, 5.66; N, 12.13.

1-(3-Chlorolphenyl)-1-methoxy(methyl)amino-1,2-dihydropyrrolo[3,4-*c*]pyridin-3-one (2e): a pale-yellow solid; mp 199–203 ˚C (hexane–CH_2Cl_2); IR (KBr) 3240, 1701, 1609 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 3H), 3.38 (s, 3H), 7.01 (br s, 1H), 7.32–7.34 (m, 2H), 7.41 (d, *J* = 4.9 Hz, 1H), 7.63–7.64 (m, 1H), 7.79 (s, 1H), 8.75 (d, *J* = 4.9 Hz, 1H), 9.06 (s, 1H); ^{13}C NMR (125 MHz) δ 36.53, 60.29, 85.33, 117.86, 123.88, 125.73, 126.11, 129.16, 130.20, 134.98, 140.12, 146.26, 152.94, 154.58, 168.72; MS *m/z* 303 (M^+, 0.47), 243 (100). Anal. Calcd for $C_{15}H_{14}ClN_3O_2$: C, 59.31; H, 4.65; N, 13.83. Found: C, 59.25; H, 4.70; N, 13.58.

1-(4-Chlorolphenyl)-1-methoxy(methyl)amino-1,2-dihydropyrrolo[3,4-*c*]pyridin-3-one (2f): a white solid; mp 87–89 ˚C (hexane–CH_2Cl_2); IR (KBr) 3219, 1709 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.40 (s, 3H), 3.37 (s, 3H), 7.01 (br s, 1H), 7.373 (d, *J* = 8.7 Hz, 2H), 7.374 (d, *J* = 5.0 Hz, 1H), 7.70 (d, *J* = 8.7 Hz, 2H), 8.74 (d, *J* = 5.0 Hz, 1H), 9.05 (s, 1H); ^{13}C NMR (125 MHz) δ 37.04, 60.30, 85.58, 117.75, 125.93, 127.22, 129.09, 134.93, 137.53, 146.23, 152.74, 155.35, 169.37; MS *m/z* 303 (M^+, 0.68), 243 (100). Anal. Calcd for $C_{15}H_{14}ClN_3O_2$: C, 59.31; H, 4.65; N, 13.83. Found: C, 59.18; H, 4.80; N, 13.55.

1-Methoxy(methyl)amino-1-(naphthalen-2-yl)-1,2-dihydropyrrolo[3,4-*c*]pyridin-3-one (2g): a white solid; mp 184–187 ˚C (hexane–CH_2Cl_2); IR (KBr) 3381, 1709 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.45 (s, 3H), 3,38 (s, 3H), 7.10 (s, 1H), 7.49–7.52 (m, 3H), 7.82–7.85 (m, 2H), 7.91 (d, *J* = 9.2 Hz, 1H), 7.98 (d, *J* = 8.6 Hz, 1H), 8.12 (s, 1H), 8.71 (d, *J* = 5.2 Hz, 1H), 9.07 (s, 1H); ^{13}C NMR (125 MHz) δ 37.19, 60.36, 85.95, 117.94, 123.56, 124.72, 125.90, 126.67, 126.78, 127.54, 128.27, 128.91, 133.08, 133.36, 136.11, 146.29 (2C), 152.71, 169.14; MS *m/z* 319 (M^+, 0.90), 259 (100). Anal. Calcd for $C_{19}H_{17}N_3O_2$: C, 71.46; H, 5.37; N, 13.16. Found: C, 71.44; H, 5.45; N, 13.16.

1-Dimethylamino-1-phenyl-1,2-dihydropyrrolo[3,4-*c*]pyridin-3-one (2h): a pale-yellow solid; mp 212–214 ˚C (hexane–$CHCl_3$); IR (KBr) 3173, 1699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.21 (s, 6H), 7.24 (br s, 1H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.36–7.40 (m, 3H), 7,72 (d, *J* = 7.3 Hz, 2H), 8.70 (d, *J* = 5.0 Hz, 1H), 9.02 (s, 1H); ^{13}C NMR (125 MH) δ 39.23, 85.34, 118.13, 125.66, 125.84, 128.84, 129.18, 139.96, 146.24, 152.76, 157.85, 169.58; MS *m/z* 253 (M^+, 0.94), 193 (100). Anal. Calcd for $C_{15}H_{15}N_3O$: C, 71.13; H, 5.97; N, 16.59. Found: C, 71.08; H, 6.01; N, 16.41.

1-(3-Chlorophenyl)-1-dimethylamino-1,2-dihydropyrrolo[3,4-*c*]pyridin-3-one (2i): a pale-yellow solid; mp 182–186 ˚C (hexane–CH_2Cl_2); IR (KBr) 3187, 1690 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.20 (s, 6H), 6.99 (br s, 1H), 7.31–7.32 (m, 2H), 7.37 (dd, *J* = 5.2, 1.1 Hz, 1H), 7.58–7.60 (m, 1H), 7.74 (s, 1H), 8.73 (d, *J* = 5.2 Hz, 1H), 9.04 (s, 1H); ^{13}C NMR (125 MHz) δ 39.23, 84.91, 118.05, 124.03, 125.49, 126.23, 129.10, 130.48, 135.30, 142.25, 146.42, 152.97, 157.21, 169.42; MS *m/z* 287 (M^+, 0.66), 227 (100). Anal. Calcd for $C_{15}H_{14}ClN_3O$: C, 62.61; H, 4.90; N, 14.60. Found: C, 62.38; H, 4.97; N, 14.41.

1-Dimethylamino-1-(3-methoxyphenyl)-1,2-dihydropyrrolo[3,4-*c*]pyridin-3-one (2j): a pale-yellow solid; mp 134–136 °C (hexane–CH_2Cl_2); IR (KBr) 3233, 1701 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 2.04 (s, 6H), 3.75 (s, 3H), 6.88 (d, *J* = 6.9 Hz, 1H), 7.21–7.30 (m, 3H), 7.62 (d, *J* = 4.6 Hz, 1H), 8.69 (d, *J* = 4.6 Hz, 1H), 8.83 (s, 1H), 9.52 (s, 1H); ^{13}C NMR (125 MHz) δ 38.76, 55.14, 84.31, 111.78, 113.61, 118.06, 118.34, 126.05, 129.96, 142.32, 145.04, 152.65, 157.30, 159.58, 168.05; MS *m/z* 283 (M^+, 0.43), 223 (100). Anal. Calcd for $C_{16}H_{17}N_3O_2$: C, 67.83; H, 6.05; N, 14.83. Found: C, 67.83; H, 6.00; N, 14.89.

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