

An efficient synthesis of 2-amino-5-chloro-3-pyridinecarboxaldehyde and 5-amino-2-chloro-4-pyridinecarboxaldehyde

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Abstract

Efficient synthetic routes to the title compounds 2-amino-5-chloro-3-pyridinecarboxaldehyde (**1a**) and 5-amino-2-chloro-4-pyridinecarboxaldehyde (**1b**) are reported. Both compounds are important substrates in the synthesis of naphthyridine derivatives.

Keywords: amino; chloro; naphthyridine; pyridinecarboxaldehyde; synthesis.

Introduction

Naphthyridine derivatives are important natural and synthetic compounds. They have received considerable attention over the past years because they have a broad spectrum of biological activities including anticancer (Atanasova et al., 2007; Bowling et al., 2008), anti-inflammatory (Roma et al., 2000, 2008), anti-hypertensive (Ferrarini et al., 2000), antiherpes (Souza et al., 2007) and antimicrobial (Pettit et al., 2004) properties. Friedländer condensation between amino pyridinecarboxaldehyde and ketones has been one of the most successful methods for the synthesis of a variety of naphthyridines (Turner, 1990; Thummel, 1992; Chen and Deady, 1993). As a part of synthesis program, we are especially interested in the synthesis of chloro and amino substituted pyridinecarboxaldehydes. Although several methods of synthesis of amino substituted pyridinecarboxaldehydes have been reported (Gassman and Huang, 1974; Majewicz and Caluwe, 1974; Turner, 1983; Moormann et al., 1987; Estel et al., 1989; Rivera et al., 2001), an efficient route to chlorinated derivatives has not been developed. Herein we would like to report an efficient and simple method for the preparation of 2-amino-5-chloro-3-pyridinecarboxaldehyde (**1a**) and 5-amino-2-chloro-4-pyridinecarboxaldehyde (**1b**).

Results and discussion

The first synthetic route to **1a** and **1b** is shown in Scheme 1. Commercially available 2-aminopyridine (**2a**) and 5-amino-2-chloropyridine (**2b**) were allowed to react with di-*tert*-butyl dicarbonate in *t*-BuOH to give the respective *N*-Boc protected products *tert*-butyl pyridin-2-ylcarbamate (**3a**) and *tert*-butyl 6-chloropyridin-3-ylcarbamate (**3b**) in high yield (Venuti et al., 1988). Lithiation (Christensen, 1975; Olah and Arvanaghi, 1981) of **3a** and **3b** with *n*-BuLi in the presence of tetramethylethylenediamine (TMEDA) in THF followed by treatment of the resultant lithio derivatives with DMF gave the respective formyl products *tert*-butyl 3-formylpyridin-2-ylcarbamate (**4a**) and *tert*-butyl 6-chloro-4-formylpyridin-3-ylcarbamate (**4b**). Removing the *N*-Bocprotecting group from **4a** and **4b** by treatment with trifluoroacetic acid (TFA) in CH₂Cl₂ gave product 2-amino-3-pyridinecarboxaldehyde (**5**) and the title compound **1b**, respectively. Compound **5** was further transformed into **1a** using *N*-chlorosuccinimide (NCS) as a halogenating reagent (Mitchell et al., 2009).

Compound **1b** was also prepared by another route (Scheme 2). Commercially available 2-chloro-4-methyl-5-nitropyridine (**6**) was converted to (*E*)-2-(2-chloro-5-nitropyridin-4-yl)-*N,N*-dimethylethanamine (**8**) by reaction with an excess of *N,N*-dimethylformamide dimethylacetal (**7**) in DMF. Oxidation (Schmitz et al., 2008) of **8** with a large excess of NaIO₄ provided 2-chloro-5-nitro-4-pyridinecarboxaldehyde (**9**) (Burger and Lindvall, 2010). Conventional reduction (Smith and Opie, 1948) of compound **9** furnished the desired product **1b**.

Conclusion

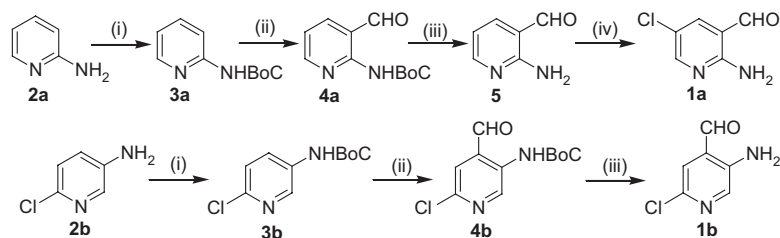
Two routes to pyridinecarboxaldehyde derivatives **1** are reported. Compounds **1a** and **1b** are important intermediates in the synthesis of naphthyridine derivatives.

Experimental section

All reactions were carried out under a nitrogen atmosphere using standard Schlenk techniques. All solvents were dried and degassed by standard methods and stored under nitrogen. ¹H NMR and ¹³C NMR spectra were recorded at 400 MHz and 100 MHz, respectively, on a Bruker DPX400 NMR spectrometer.

Tert-butyl pyridin-2-ylcarbamate (**3a**)

To a stirred solution of **2a** (9.4 g, 0.1 mol) in *t*-BuOH (200 ml) was added di-*tert*-butyl dicarbonate (24 g, 0.11 mol). The mixture was



Reagents and conditions: (i) (Boc)₂O, *t*-BuOH, 30–40°C, overnight; (ii) -78°C, *n*-BuLi, 30 min, TMEDA, -78–0°C, 2 h, DMF, -78°C–rt., overnight; (iii) TFA, CH₂Cl₂, rt., overnight; (iv) NCS, CH₃CN, refluxing, 2 h

Scheme 1 Synthesis of compound **1a** and **1b**.

stirred overnight at 30–40°C. Solvent was evaporated in vacuo to give crude product **3a** which was further purified by crystallization from ethanol. A white solid (16.0 g, yield 83%) was obtained; mp 79–81°C ¹H NMR (CDCl₃): δ 1.55 (s, 9H), 6.92–6.95 (m, 1H), 7.64–7.68 (m, 1H), 7.99–8.01 (m, 1H), 8.30–8.35 (m, 1H), 8.78 (s, 1H); ¹³C NMR (CDCl₃): δ 28.0, 80.2, 112.3, 117.4, 137.9, 147.1, 152.7.

Compound **3b** was obtained as a white solid by using a similar procedure (yield 80%); mp 127–128°C. ¹H NMR (CDCl₃): δ 1.50 (s, 9H), 6.88–7.01 (m, 1H), 7.24 (d, *J*=8.8 Hz, 1H), 7.93 (s, 1H), 8.27 (s, 1H); ¹³C NMR (CDCl₃): δ 28.2, 81.3, 124.1, 128.9, 134.9, 139.7, 144.2, 152.9.

Tert-butyl 3-formylpyridin-2-ylcarbamate (4a)

To a stirred solution of **3a** (1.94 g, 10 mmol) in dry THF (20 ml) at -78°C was added dropwise *n*-BuLi in *n*-hexane (12 ml, 2.5 M, 30 mmol). The solution was stirred at the same temperature for 30 min and then TMEDA (0.9 ml, 3 mmol) was added. The mixture was allowed to warm slowly to -20°C and stirred for 2 h. Excess DMF (5 ml) was then added at -78°C. The resultant mixture was warmed to room temperature slowly, stirred overnight and then quenched with a saturated aqueous solution of NaHCO₃. The mixture was then extracted with CH₂Cl₂, and the extract was dried over anhydrous sodium sulfate, filtered, and concentrated to give a yellow oil. Purification by silica gel column chromatography (CH₂Cl₂/ethyl acetate, 10:1) gave **4a** as a white solid (1.0 g, yield 45%); mp 111–112°C; ¹H NMR (CDCl₃): δ 1.56 (s, 9H), 7.12–7.15 (m, 1H), 7.99–8.02 (m, 1H), 8.65–8.67 (m, 1H), 9.92 (s, 1H), 10.18 (s, 1H); ¹³C NMR (CDCl₃): δ 28.0, 81.4, 116.8, 117.7, 143.6, 150.6, 152.3, 154.1, 192.8.

Compound **4b** was obtained as a white solid by using a similar procedure (yield 40%); mp 146–148°C; ¹H NMR (CDCl₃): δ 1.54 (s, 9H), 7.55 (s, 1H), 9.61 (s, 1H), 9.76 (s, 1H), 9.45 (s, 1H); ¹³C NMR (CDCl₃): δ 30.9, 84.9, 129.7, 129.9, 137.5, 145.0, 146.5, 154.8, 196.1.

5-Amino-2-chloro-4-pyridinecarboxaldehyde (1b)

To a stirred solution of **4b** (2.57 g, 10 mol) in CH₂Cl₂ (100 ml) was added TFA (10 ml) at room temperature. The mixture was stirred overnight and then saturated aqueous NaHCO₃ solution was added. It was then extracted with CH₂Cl₂ and dried over anhydrous sodium sulfate, filtered and concentrated to give yellow oil which was further purified by silica gel column chromatography (CH₂Cl₂/ethyl acetate, 10:1) to give 1.5 g (96%) of **1b** as a yellow solid; mp 164–166°C; ¹H NMR (DMSO-*d*₆): δ 7.15 (br, 2H), 7.64 (s, 1H), 8.07 (s, 1H), 9.92 (s, 1H); ¹³C NMR (DMSO-*d*₆): δ 123.5, 126.7, 135.2, 141.0, 144.3, 194.4. HRMS: Calculated for C₆H₅ClN₂O: 156.0090; Found: 156.0089.

Compound **5** was obtained as a yellow solid by using a similar procedure: yield 40%; mp 84–86°C; ¹H NMR (CDCl₃): δ 6.73–7.04 (m+br, 3H), 7.80–7.82 (m, 1H), 8.26–8.27 (m, 1H), 9.86 (s, 1H); ¹³C NMR (CDCl₃): δ 112.6, 113.7, 144.3, 154.5, 158.5, 192.6.

2-Amino-5-chloro-3-pyridinecarboxaldehyde (1a)

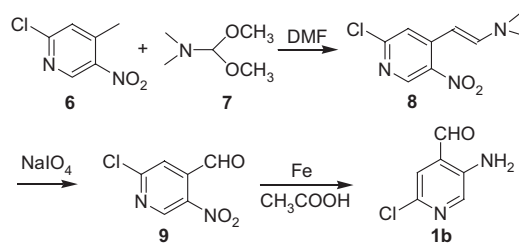
To a stirred solution of **5** (0.97 g, 8 mmol) in acetonitrile (20 ml) was added NCS (2.14 g, 16 mmol). The mixture was heated under reflux for 2 h. Solvent was evaporated in vacuo to give the crude product which was further purified by silica gel column chromatography (CH₂Cl₂/ethyl acetate, 10:1). Product **1a** was obtained as a yellow solid (0.65 g, yield 52%); mp 162–164°C; ¹H NMR (DMSO-*d*₆): δ 7.68 (s, 2H), 8.15 (s, 1H), 8.26 (s, 1H), 9.84 (s, 1H); ¹³C NMR (DMSO-*d*₆): δ 113.9, 119.3, 142.6, 153.4, 155.5, 191.5. HRMS: calculated for C₆H₅ClN₂O: 156.0090; Found: 156.0088.

(E)-2-(2-chloro-5-nitropyridin-4-yl)-*N,N*-dimethylethanamine (8)

To a stirred solution of 2-chloro-4-methyl-5-nitropyridine (**6**, 8.6 g, 0.05 mol) in excess DMF (12.9 ml) was added *N,N*-dimethylformamide dimethylacetal (**7**, 16.6 ml, 0.125 mol). The mixture was heated at 145°C for 2 h and then concentrated to give a dark solid. Crystallization from ethyl acetate gave product **8** as a red solid; mp 191–193°C; ¹H NMR (CDCl₃): δ 3.06 (s, 6H), 5.95 (d, *J*=13.1 Hz, 1H), 7.26 (d, *J*=7.8 Hz, 1H), 7.33 (d, *J*=13.1 Hz, 1H), 8.79 (s, 1H).

2-Chloro-5-nitro-4-pyridinecarboxaldehyde (9)

To a stirred solution of compound **8** (4.55 g, 0.02 mol) in a mixture of THF (100 ml) and H₂O (100 ml) was added NaIO₄ (17.11 g, 0.08 mol). The mixture was stirred at room temperature overnight while the dark solution became pale yellow with a heavy precipitate.



Scheme 2 Synthesis of compound **1b**.

The solid material was filtered off, washed twice with ethyl acetate and the organic phase was concentrated to give the crude product which was further purified by silica gel column chromatography (hexane/ethyl acetate, 3:1). The product is a yellow solid; mp 165–167°C; ¹H NMR (CDCl₃): δ 7.76 (s, 1H), 9.25 (s, 1H), 10.50 (s, 1H).

5-Amino-2-chloro-4-pyridinecarboxaldehyde (1b)

Compound **1b** was synthesized from compound **9** using the reported procedure (Smith and Opie, 1948).

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References

- Atanasova, M.; Ilieva, S.; Galabov, B. QSAR analysis of 1,4-dihydro-4-oxo-1-(2-thiazolyl)-1,8-naphthyridines with anticancer activity. *Eur. J. Med. Chem.* **2007**, *42*, 1184–1192.
- Bowling, J. J.; Pennaka, H. K.; Ivey, K.; Wahyuono, S.; Kelly, M.; Schinazi, R. F.; Valeriote, F. A.; Graves, D. E.; Hamann, M. T. Antiviral and anticancer optimization studies of the DNA-binding marine natural product aaptamine. *Chem. Biol. Drug Des.* **2008**, *71*, 205–215.
- Burger, M.; Lindvall, M. Bicyclic kinase inhibitors. *WO2010026121*.
- Chen, Q.; Deady, L. W. Synthesis of some benzo[*b*][1,6]naphthyridines and benzo[*b*][1,7]naphthyridines. *Aust. J. Chem.* **1993**, *46*, 987–993.
- Christensen, H. Preparation of salicylaldehydes via the ortho-lithio derivatives of methoxymethyl-protected phenols. *Synth. Commun.* **1975**, *5*, 65–78.
- Estel, L.; Linard, F.; Marsais, F.; Godard, A.; Quéguiner, G. Synthesis of ortho-substituted aminopyridines. Metalation of pivaloyl-amino derivatives. *J. Heterocyclic Chem.* **1989**, *26*, 105–112.
- Ferrarini, P. L.; Mori, C.; Badawneh, M.; Calderone, V.; Greco, R.; Manera, C.; Martinelli, A.; Nieri, P.; Saccomanni, G. Synthesis and β-blocking activity of (*R*, *S*)-(*E*)-oximeethers of 2,3-dihydro-1,8-naphthyridine and 2,3-dihydrothiopyrano [2,3-*b*] pyridine: potential antihypertensive agents – Part IX. *Eur. J. Med. Chem.* **2000**, *35*, 815–826.
- Gassman, P. G.; Huang, C. T. Selective formylation of 2-aminopyridines. *J. Chem. Soc. Chem. Comm.* **1974**, 685–686.
- Majewicz, T. G.; Caluwe, P. A facile synthesis of 2-amino-nicotinaldehyde. *J. Org. Chem.* **1974**, *39*, 720–721.
- Mitchell, G.; Salmon, R.; Bacon, D. P.; Pinall, I. H.; Briggs, E.; Avery, A. J.; Morris, J. A.; Russell, C. J. Herbicidal compounds. *WO2009115788*.
- Moormann, A. E.; Yen, C. H.; Yu, S. A facile synthesis of 2-amino-nicotinaldehyde. *Synth. Commun.* **1987**, *17*, 1695–1699.
- Olah, G. A.; Arvanaghi, M. Aldehydes by formylation of Grignard or organolithium reagents with *N*-formylpiperidine. *Angew. Chem. Int. Ed.* **1981**, *20*, 878–879.
- Pettit, G. R.; Hoffmann, H.; McNulty, J.; Higgs, K. C.; Murphy, A.; Molloy, D. J.; Herald, D. L.; Williams, M. D.; Pettit, R. K.; Doubek, D. L.; et al. Antineoplastic agents. 380. Isolation and X-ray crystal structure determination of isoaptamine from the Republic of Singapore *hymeniacidon* sp. and conversion to the phosphate prodrug hystatin 1. *J. Nat. Prod.* **2004**, *67*, 506–509.
- Rivera, N. R.; Hsiao, Y.; Cowen, J. A.; McWilliams, C.; Armstrong, J.; Yasuda, N.; Hughes, D. L. Highly efficient synthesis of 2-amino-3-pyridinecarboxaldehyde. *Synth. Commun.* **2001**, *31*, 1573–1579.
- Roma, G.; Braccio, M. D.; Grossi, G.; Mattioli, F.; Chia, M. 1,8-Naphthyridines IV. 9-Substituted N,N-dialkyl-5-(alkylamino or cycloalkylamino) [1,2,4]triazolo[4,3-*a*] [1,8]naphthyridine-6-carboxamides, new compounds with anti-aggressive and potent anti-inflammatory activities. *Eur. J. Med. Chem.* **2000**, *35*, 1021–1035.
- Roma, G.; Grossi, G.; Braccio, M. D.; Piras, D.; Ballabeni, V.; Tognolini, M.; Bertoni, S.; Barocelli, E. 1,8-Naphthyridines VII. New substituted 5-amino [1,2,4]triazolo[4,3-*a*][1,8]naphthyridine-6-carboxamides and their isosteric analogues, exhibiting notable anti-inflammatory and/or analgesic activities, but no acute gastrotoxicity. *Eur. J. Med. Chem.* **2008**, *43*, 1665–1680.
- Schmitz, F. U.; Roberts, C. D.; Griffith, R. C.; Botyanszki, J.; Pham, S. M. Antiviral agents. *WO2008008907*.
- Smith, L. I.; Opie, J. W. *o*-Aminobenzaldehyde. *Org. Synth.* **1948**, *28*, 11.
- Souza, T. M. L.; Abrantes, J. L.; Epifanio, R. A.; Fontes, C. F. L.; Frugulhetti, I. C. P. P. The alkaloid 4-methylaaptamine isolated from the sponge *aaptos aaptos* impairs *herpes simplex* virus type 1 penetration and immediate-early protein synthesis. *Planta Med.* **2007**, *73*, 200–205.
- Thummel, R. P. The application of Friedländer and Fischer methodologies to the synthesis of organized polyaza cavities. *Synlett* **1992**, 1–12.
- Turner, J. A. Regiospecific electrophilic substitution of aminopyridines: ortho lithiation of 2-, 3-, and 4-(pivaloylamino)-pyridines. *J. Org. Chem.* **1983**, *48*, 3401–3408.
- Turner, J. A. A general approach to the synthesis of 1,6-, 1,7- and 1,8-naphthyridines. *J. Org. Chem.* **1990**, *55*, 4744–4750.
- Venuti, M. C.; Stephenson, R. A.; Alvarez, R.; Bruno, J. J.; Strosberg, A. M. Inhibitors of cyclic AMP phosphodiesterase 3. Synthesis and biological evaluation of pyrido and imidazolyl analogs of 1,2,3,5-tetrahydro-2-oxoimidazo [2,1-*b*] quinazoline. *J. Med. Chem.* **1988**, *31*, 2136–2145.

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