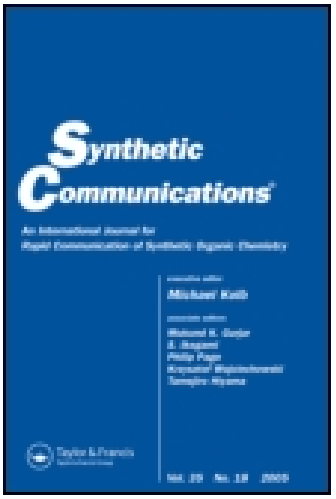

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

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Accepted author version posted online: 29 Feb 2012.Published online: 21 Feb 2013.

To cite this article: Helena Majgier-Baranowska, Bing Li & Norton P. Peet (2013) Efficient Synthesis of tert-Butyl (6-Formylpyridin-2-yl)carbamic Acid, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 43:8, 1173-1180, DOI: 10.1080/00397911.2011.625291

To link to this article: http://dx.doi.org/10.1080/00397911.2011.625291

Synthetic Communications®, 43: 1173–1180, 2013

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2011.625291

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EFFICIENT SYNTHESIS OF *tert*-BUTYL (6-FORMYLPYRIDIN-2-yl)CARBAMIC ACID

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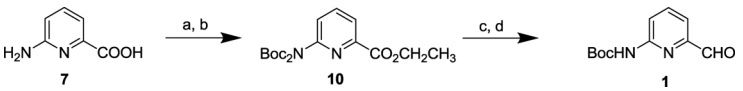
Microbiotix, Inc., Worcester, Massachusetts, USA

GRAPHICAL ABSTRACT



Abstract *We have developed an efficient four-step synthesis of* tert-*butyl (6-formylpyridin-2-yl)carbamic acid (**1**) in 80% overall yield using inexpensive starting material and reagents and no air-sensitive reagents. Column chromatography was not required for purification of the intermediates or the final product.*

Keywords 6-Aminopyridine-2-carboxaldehyde; 6-aminopyridine-2-carboxylic acid; bis-Boc protection; building block synthesis; carbamate protection

INTRODUCTION

Pyridine is frequently found as the core structure or a component in a variety of drugs, for example, ethionade,[1] etoricoxib,[2] dimetindene,[3] brompheniramine,[4] isoniazid,[5] and metyrapone[6] (Fig. 1). Consequently, there has been significant effort directed toward the design of new and efficient syntheses for pyridine-containing building blocks.[7]

The specific pyridine-containing building block that we required for preparation of a designed compound library was *tert*-butyl (6-formylpyridin-2-yl)carbamic acid (**1**), as shown in Scheme 1, which was quite expensive and commercially available only in small quantities from limited sources (CAS number: 956523-98-1). The synthesis of compound **1** has been previously reported[8a] starting from 2-amino-6-bromopyridine (**2**) as shown in Scheme 1. Boc-protection of the amino group of 2-amino-6-bromo-pyridine (**2**) gave an inseparable mixture of mono-Boc-protected compound **3** and di-Boc-protected compound **4**, in a ratio of 4:1. The mixture of mono-Boc and di-Boc esters **3** and **4** was treated with *i*-PrMgCl•LiCl to give mono-Boc-protected compound **3** in 68% yield. Treatment of compound **3** with methyllithium and

Received September 12, 2011.

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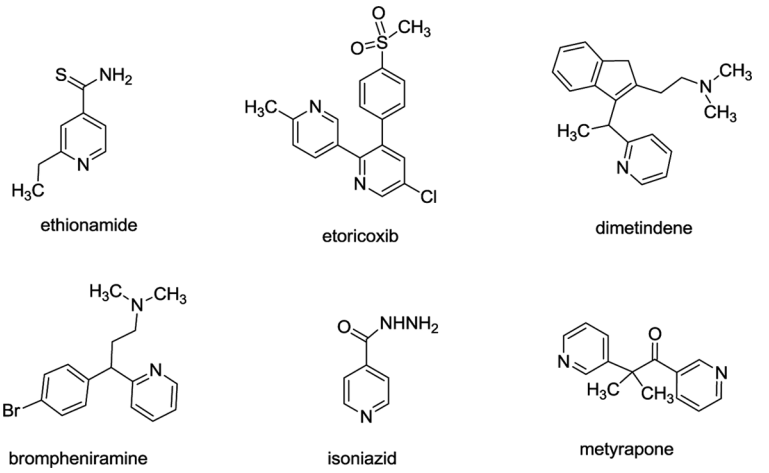
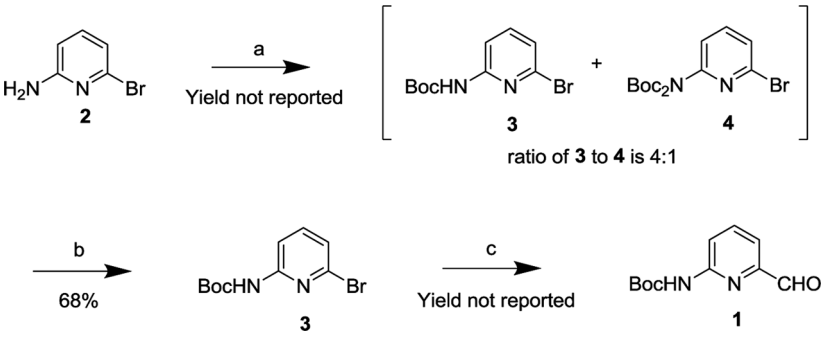


Figure 1. Structures of selected pyridine-containing drugs.

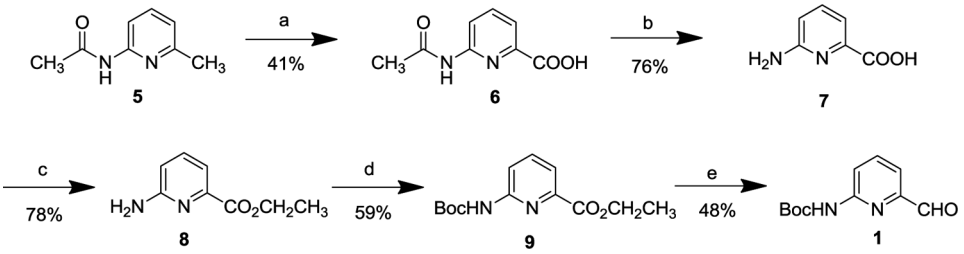
n-butyllithium to produce the metallated dianion, followed by treatment with dimethylformamide (DMF), provided compound **1** (yield and ^{1}H NMR spectra were not reported). Even though the reported synthesis is only three steps, this procedure requires an expensive starting material and air-sensitive magnesium and lithium reagents, chromatography is required, and the overall yield is poor.

Shown in Scheme 2 is an alternate, lengthier procedure reported[8b] for the preparation of aldehyde **1**. This procedure was not attractive to us because of its length and overall poor yield. Starting with 2-acetamido-6-methylpyridine (**5**), which is also costly from many suppliers, the five-step procedure gives only 6.9% yield of aldehyde **1**. It was clear, therefore, that a new, concise procedure that did not use expensive starting materials or reagents, or air-sensitive reagents, and that was amenable to large-scale production was needed.

To prepare multigram quantities of building block **1** to support the preparation of our focused library, we developed a new synthesis, which is efficient and



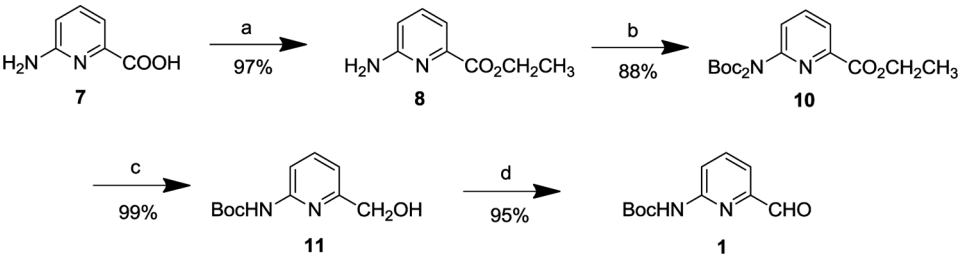
Scheme 1. Literature synthesis of compound **1**.[8a] Reagents and conditions: (a) $(Boc)_2O$, DMAP, TEA, DCM, 0 °C, 5 h, column chromatography; (b) *iso*-PrMgCl·LiCl, THF, 0 °C, 30 min; and (c) CH_3Li, and then *n*-BuLi, DMF, THF, −78 °C, 30 min and then 1 h, rt.



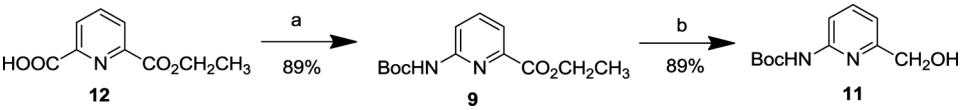
Scheme 2. Literature synthesis of compound **1**.[10b] Reagents and conditions: (a) $KMnO_4$, water, 80 °C; (b) 2 M NaOH, reflux, 180 min; (c) H_2SO_4, EtOH, reflux, 23 h; (d) $(Boc)_2O$, Et_3N, THF, 60 °C, 9 h, column chromatography; and (e) DIBAL, THF, −78 °C, column chromatography.

cost-effective, requires no chromatography, is scalable, and high yielding, and importantly avoids air-sensitive reagents. This synthesis, which contains an important and rather unusual bis-Boc intermediate (compound **10**), is shown in Scheme 3.

We envisioned that esterification of 6-amino-2-picolinic acid (**7**) would proceed smoothly to produce 6-amino-2-picolinic acid ethyl ester (**8**) as shown in Scheme 3. Indeed, by employing a modified procedure where 6-amino-2-picolinic acid (**7**) was treated with $SOCl_2$ in absolute EtOH at reflux[9c] for 72 h, we obtained the corresponding ester **8** as a hydrochloride salt in 97% yield.[9a,b] Preparation of compound **8** from **7** has also been reported by using the following conditions: 4 N HCl in 1,4-dioxane,[9d] HCl[9e] or oxalyl chloride in dichloromethane (DCM),[9f] and H_2SO_4[9g] followed by EtOH. All of these procedures give modest yields of esterified product. The corresponding methyl ester has also been synthesized using methanolic hydrogen chloride.[9h] Our efforts to obtain ethyl 6-[(*tert*-butyloxycarbonyl)amino]-2-picolinic acid (**9**) from ester **8** (Scheme 2) using reported conditions[9c] were unsuccessful; a mixture of compounds was produced, which contained mono-Boc and di-Boc products, as well as the starting material **8**. The mono-Boc and di-Boc product mixture was extremely difficult to separate using silica-gel column chromatography. However, we noticed that reduction of a mixture of mono-Boc and di-Boc esters with a metal hydride led solely to mono-Boc alcohol **11**. Therefore, we decided to directly prepare the di-Boc compound **10** and then reduce the ester group to directly produce alcohol **11**, which would be the immediate precursor to the desired aldehyde **1**, as shown in Scheme 3.



Scheme 3. New synthesis of compound **1**. Reagents and conditions: (a) $SOCl_2$, EtOH, reflux 72 h; (b) *tert*-BuOH, acetone, $(Boc)_2O$, DMAP, rt, 77 h; (c) $NaBH_4$, $CaCl_2$, EtOH, 0 °C, 90 min, and then rt, 90 min; and (d) pyridine-SO_3, DMSO-CH_2Cl_2 (1:4), rt, 90 min.



Scheme 4. Literature synthesis of compound **11**.[10a] Reagents and conditions: (a) DPPA, TEA, *tert*-BuOH, toluene, 100 °C, overnight, column chromatography; and (b) $CaCl_2$, $NaBH_3CN$, EtOH, 0 °C, 2 h.

Treatment of compound **8** with Boc anhydride, in the presence of dimethylaminopyridine (DMAP), either in an acetone/*tert*-BuOH solution or in dichloromethane, produced only bis-Boc intermediate **10**, in 88% or 82% yield, respectively. The product was recovered by crystallization from the reaction mixture, at low temperatures, and no mono-Boc-protected product was detected after crystallization. Next, compound **10** was treated with $Ca(BH_4)_2$, generated in situ from $CaCl_2$ and $NaBH_4$, in absolute EtOH at 0 °C to give the corresponding *tert*-butyl [6-(hydroxymethyl)pyridin-2-yl]carbamic acid (**11**) in 99% yield. Note that under the reduction conditions, the di-Boc-protected amino group was simultaneously transformed to the mono-Boc-protected amino group.

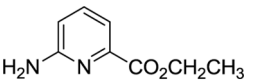
Synthesis of compound **11** has previously been reported[10a] using several approaches, starting from expensive 6-(ethoxycarbonyl)-2-picolinic acid (**12**, CAS number: 21855-16-3) with variable yields. For example, under Curtis rearrangement conditions, compound **12** was converted to ethyl 6-[(*tert*-butyloxycarbonyl)amino]-2-picolinic acid (**9**); subsequent treatment of **9** with $NaBH_3CN/CaCl_2$ efficiently reduced the ester to produce alcohol **11** (quantitative yield).[10a] Other reduction conditions for the conversion of **9** to **11** have also been used,[10b–e] including $NaBH_4/CaCl_2$[10b,c] and $LiAlH_4$.[9a] Synthesis of alcohol **11** has also been reported from aldehyde **1** by reduction with $NaBH_4$.[8a]

Our attempt to oxidize alcohol **11** to aldehyde **1** with the Dess–Martin reagent was inefficient; only 9% of the desired compound **1** was produced. Finally, the corresponding aldehyde **1** was obtained in excellent yield (95%) from oxidation of alcohol **11** at room temperature in dimethylsulfoxide (DMSO)–CH_2Cl_2 (1:4) by employing the inexpensive Parikh–Doering reagent (pyridine-SO_3)[11] in the presence of Et_3N. The final crude product **1** was purified simply by elution with 2:3 EtOAc–hexanes through a plug of silica gel to remove traces of pyridine.

In summary, we have developed a practical and efficient four-step synthesis of *tert*-butyl (6-formylpyridin-2-yl)carbamic acid (**1**) in 80% overall yield. The synthesis started from inexpensive 6-amino-2-picolinic acid (**7**). All four synthetic steps were performed with inexpensive, non-air-sensitive chemical reagents, and purification of the intermediates and the final product avoided silica-gel column chromatography. Compound **1** is a useful two-point scaffold and building block for the synthesis of compound libraries with potential biological activity.

EXPERIMENTAL

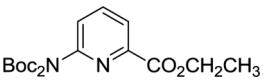
Ethyl 6-Amino-2-picolinic Acid (8)



8

A heterogeneous mixture of 6-amino-2-picolinic acid (**7**) (25 g, 0.181 mol) in absolute ethanol (190 mL) was cooled in an acetone–dry ice bath (0 °C) and carefully treated with $SOCl_2$ (15 mL) under an argon atmosphere with stirring. The reaction mixture was heated in an oil bath at 85 °C. Additional $SOCl_2$ was added to the reaction mixture after 21 h (16 mL) and 45 h (10 mL), and heating was continued for an additional 24 h. The reaction mixture was cooled to rt, diluted with ethyl ether (200 mL), and stored in a refrigerator (+5 °C) overnight. The solid that formed was collected by filtration, washed with ethyl ether, and air dried to give a cream-colored solid as the hydrochloride salt of **8**. This hydrochloride salt was suspended in CH_2Cl_2 and treated with saturated aqueous $NaHCO_3$ until the phases were clear. The organic layer was separated, washed with water and brine, dried over Na_2SO_4, and co-evaporated with hexanes, and the residue was triturated with hexanes and collected to give **8** as a cream-colored solid (24.69 g, 97%), $R_f = 0.33$ (1:1 EtOAc–hexanes), mp 115.7–116.2 °C, LC/MS/m/z 166 (M + 1). ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 7.56$–7.45 (m, 2H), 6.67 (dd, $J = 0.9$, 8.1 Hz, 1H), 4.94 (bs, 2H), 4.42 (q, $J = 7.2$ Hz, 2H), 1.41 (t, $J = 7.2$ Hz, 3H) (reported ^{1}H NMR spectrum at 400 MHz).[9i]

Ethyl Bis-(*N,N-tert*-butyloxycarbonyl)-6-amino-2-picolinic Acid (10)



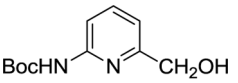
10

Method A. A mixture of ethyl 6-amino-2-picolinic acid (**8**) (19.0 g, 114 mmol), *tert*-BuOH (100 mL) and acetone (65 mL) was treated with DMAP (2.79 g, 228 mmol) and a solution of di-*tert*-butyl dicarbonate (53.9 g, 247 mmol) in *tert*-BuOH (35 mL) and stirred at room temperature for 48 h. The reaction mixture was diluted with hexanes (600 mL) and cooled to −60 °C for 3 h. A white solid was collected by filtration, washed with cold hexanes, and dried in air. The filtrate was evaporated to dryness. The residue was dissolved in a minimal amount of CH_2Cl_2, diluted with hexanes, and cooled to −20 °C. The second crop was collected by filtration, washed with cold hexanes to give, in total, **10** as a white solid (36.8 g, 88%), $R_f = 0.75$ (1:1 EtOAc–hexanes), mp 112–116 °C; LC/MS/m/z 367.4 (M + 1). ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 8.03$ (d, $J = 7.8$ Hz, 1H), 7.87 (t, $J = 8.1$ Hz), 7.47 (d, $J = 7.2$ Hz), 4.45 (q, $J = 7.2$ Hz, 2H), 1.46 (s, 18H), 1.41 (t, $J = 6.9$ Hz, 3H).

Method B. Di-*tert*-butyl dicarbonate (1.24 g, 5.68 mmol) and DMAP (63 mg, 0.534 mmol) were added to a stirred solution of 6-amino-2-picolinic acid ethyl ester (**8**) (300 mg, 1.80 mmol) in CH_2Cl_2 (5 mL). After stirring for 18 h, additional di-*tert*-butyl dicarbonate (169.1 mg, 0.775 mmol) was added, and stirring was continued for 12 h. Additional di-*tert*-butyl dicarbonate (170.4 mg, 0.781 mmol) was again added, and stirring was continued for another 12 h. The solution was passed through a pad of silica gel and concentrated. The solid residue was dissolved in a minimum volume of hexanes and refrigerated (+5 °C) overnight to give white crystals that were collected by filtration and dried in air and then under high vacuum to give compound **10** as a white powder (0.541 g, 1.48 mmol, 82%), $R_f = 0.75$ (1:1 EtOAc–hexanes),

mp 112 – 116 °C; LC/MS/m/z 367.4 (M + 1). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.02 (d, J = 7.8 Hz, 1H), 7.86 (t, J = 7.8 Hz), 7.47 (d, J = 8.1 Hz, 1H), 4.45 (q, J = 7.2 Hz, 2H), 1.46 (s, 18H), 1.41 (t, J = 6.9 Hz, 3H).

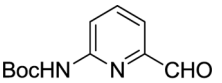
tert-Butyl [6-(Hydroxymethyl)pyridin-2-yl]carbamic Acid (11)



11

A sonicated suspension of 93% $CaCl_2$ (12.1 g, 109 mmol) in EtOH (70 mL) was added followed by the portionwise addition of solid $NaBH_4$ (10.3 g, 273 mmol), sequentially, over 20 min to a solution of ethyl bis-(*N,N-tert*-butyloxycarbonyl)-6-amino-2-picolinic acid (**10**) (10 g, 27.3 mol) in absolute ethanol (250 mL) cooled in an ice-water bath. The heterogeneous mixture was stirred at 0 °C for 90 min and then at room temperature for an additional 90 min. The suspension was filtered, and the precipitate was washed with absolute ethanol. The filtrate was evaporated to give a transparent, gelatinous residue. The residue was dissolved in $CHCl_3$ and washed with 1 N NaOH. The resulting white suspension was filtered, and the precipitate was washed with chloroform. The filtrate was extracted with chloroform, and the combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated to give a glassy residue **11** (6.05 g, 99%), R_f = 0.56 (1:1 EtOAc–hexanes), LC/MS/m/z 255.4 (M + 1). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.82 (d, 8.4 Hz, 1H), 7.65 (t, J = 7.8 Hz, 1H), 7.23 (bs, 1H), 6.89 (dd, J = 0.6, 7.5 Hz, 1H), 4.65 (d, J = 4.8 Hz, 2H), 3.40 (t, J = 5.1 Hz, 1H), 1.53 (s, 9H) (reported ^{1}H NMR).[10c]

tert-Butyl (6-Formylpyridin-2-yl)carbamic Acid (1)



1

Et_3N (17.3 mL) followed by the portionwise addition of pyridine-SO_3 (11.9 g, 74.8 mmol) was added at rt to a stirred solution of *tert*-butyl (6-(hydroxymethyl) pyridin-2-yl)carbamic acid (**11**) (5.58 g, 24.9 mmol) in CH_2Cl_2 (250 mL) and dry DMSO (62 mL). Stirring was continued for 1.5 h, and the reaction solution was quenched with water (600 mL) and extracted with EtOAc (4 × 600 mL). The organic layer was washed with water and brine, dried over Na_2SO_4, and evaporated to give a crude product. The crude product was applied to a thick pad of silica and eluted with 2:3 EtOAc–hexanes to remove a trace of pyridine. Evaporation of the solvents gave the desired product **1** as a honey-colored solid (5.26 g, 95%), R_f = 0.66 (2:3 EtOAc–hexanes), mp 156 °C (dec). LC/MS/m/z 224 (M + 1). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.89 (s, 1H), 8.20 (d, J = 8.4 Hz, 1H), 7.84 (t, J = 7.5 Hz, 1H), 7.62 (dd, J = 0.6, 7.5, 1H), 7.48 (bs, 1H), 1.54 (s, 9H) (reported ^{1}H NMR at 400 MHz).[8b]

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