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Direct synthesis of Cbz-protected (2-amino)-6-(2-aminoethyl)pyridines

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ABSTRACT

A novel series of (2-amino)-6-(2-aminoethyl)pyridines were prepared by a convenient Suzuki–Miyaura coupling approach from 2-amino-6-bromopyridines. Benzyl vinylcarbamate was first treated with 9-BBN followed by aqueous NaOH and then the appropriate bromopyridine precursors were added into the mixture. The mixture was finally heated in presence of a palladium catalyst to provide the corresponding products in overall high yields. The procedure is extended to the preparation of related pyrazine and pyrimidine compounds as well as (2-amido)- and (2-alkoxy)-6-(2-aminoethyl)pyridines.

1. Introduction

The 2-amino-6-(2-aminoethyl)pyridine skeleton **1** (Fig. 1) is an important structural motif found in various medicinally important molecules.[1] In particular, 2-aminopyridine derivatives (e.g., compound **1a**) are potent inhibitors of nitric oxide synthase (NOS) and thus could be used in the treatment of NOS-related diseases e.g., inflammation, septic shock, rheumatoid arthritis, osteoarthritis, Parkinson's disease, cardiovascular diseases, allergy, cancer, obesity and pain.[2] 2-Aminopyridines have also been shown to inhibit apolipoprotein B (Apo B) secretion and therefore are potentially useful in the conditions associated with elevated circulating levels of Apo B, such as hyperlipidemia, hypertriglyceridemia, atherosclerosis, restenosis, pancreatitis, non-insulin dependent diabetes mellitus and coronary heart diseases.[3] Trovirdine (**1b**), a known HIV-1 reverse transcriptase inhibitor, contains a 2-(2-aminoethyl)-pyridine subunit.[4] In spite of these interesting biological activities, only a limited number of synthetic approaches have appeared in literature to date for the synthesis of compounds related to **1** and therefore, a convenient and general route for the synthesis of this heterocyclic skeleton continues to be of great synthetic interest.

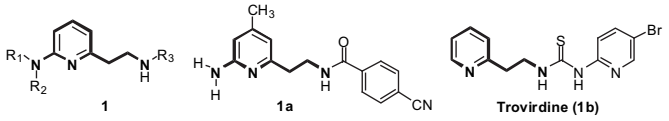

Figure 1. (2-Aminoethyl)pyridines.

As a part of an ongoing research program, we recently found the need to develop a convenient and general route for the synthesis of various *N*-protected (2-aminoethyl)heterocyclic compounds related to structure **1**. Several routes were envisioned for the synthesis of these 2-(2-aminoethyl)pyridines (Fig. 2). For example, the synthesis of the desired compounds could be accomplished by the addition of amines (or phthalimides)[5a,6] to 2-vinylpyridines, made in turn from either 2-halopyridines or related 2-substituted pyridine derivatives (*path a*).[5] However, the literature shows that low yield of the desired product was encountered in many cases[5b,c,7] possibly due to the formation of the bis-addition product as one of the major byproducts.[8] Alternatively, Heck reactions using an acrylate followed by subsequent manipulations could afford **1** (*path b*).[9] Another route could be accomplished by the reduction of the (2-cyanomethyl)pyridines that can be made directly either from the corresponding 2-bromopyridines[10] or by multiple steps via the intermediacy of alkyl cyano(2-pyridinyl)acetates[11] or 2-halomethylpyridines (*path c*).[12] Also, these 2-(2-aminoethyl)pyridines could be synthesized from 2-(2-nitrovinyl)pyridines that, in turn, could be prepared from 2-pyridinecarboxaldehydes using the Henry reaction conditions (*path d*).[13]

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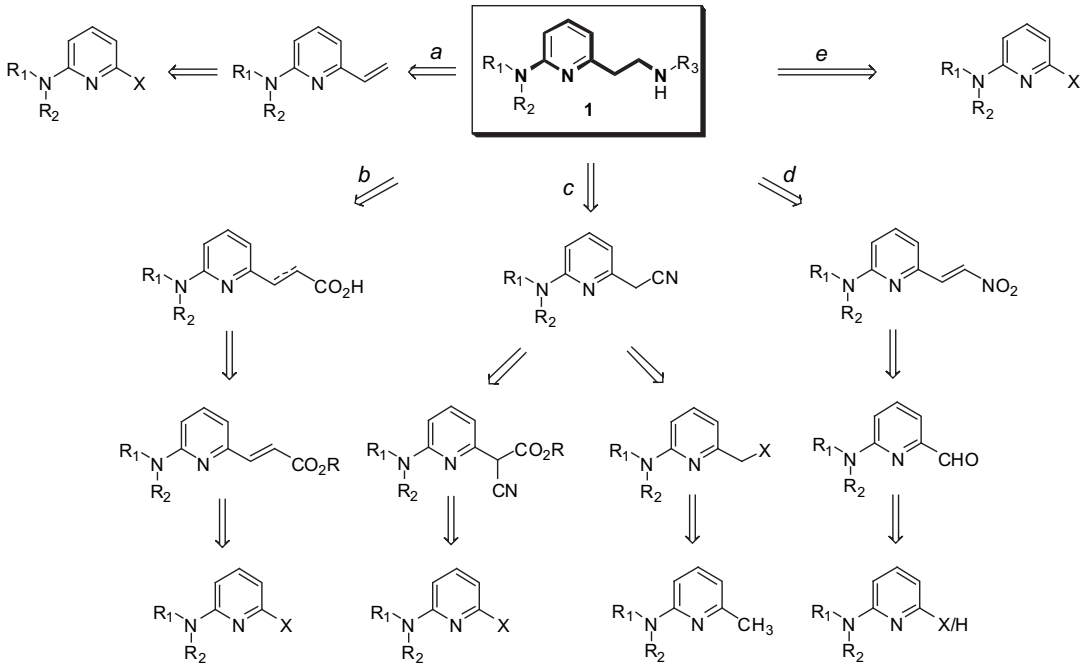


Figure 2. Possible synthetic routes to (2-aminoethyl)pyridines.

Apart from the aforementioned methods, modern metal-catalyzed cross-coupling reactions such as those developed by Negishi or Kumada,[14] or some variant of the Suzuki–Miyaura reactions[15] are attractive alternatives to attain this synthetic transformation (*path e*). Although rhodium-catalyzed hydroamination reactions of vinylpyridines[16a] and photo-catalyzed [2+2+2]-cycloaddition reactions of nitriles with acetylenes[16b] are known, these were not considered practical for our purposes.

Few reports have appeared in the literature to show that a halo-heterocycle may be *directly* converted into the corresponding *N*-protected (2-aminoethyl)heterocycle (**1**, R_3=protecting group) using a Suzuki–Miyaura cross-coupling method. This has been achieved either by direct cross-coupling of a dialkylborane intermediate (generated in situ from benzyl *N*-vinylcarbamate)[17–19] or a β-aminoethyltrifluoroborate (made separately)[20] with the heteroaryl iodides or bromides. The original report by Kamatani and Overman, however, describes only one example of this β-aminoethylation reaction involving a heterocycle where a simple 4-bromopyridine is converted to the corresponding β-aminoethyl derivative.[18] Interestingly, even after a decade, not much activity and development have been observed using this reaction in the field of heterocyclic chemistry and just a few examples were found where similar β-aminoethylation was achieved with halides directly attached to the ring bearing the heteroatom.[19] Although recent reports by Molander and co-workers describe a similar transformation with several bromo-heterocycles, including unsubstituted 3-bromopyridine, the preparation of prerequisite potassium β-aminoethyltrifluoroborate itself involves multiple synthetic manipulations. Moreover, the final palladium-catalyzed cross-coupling reaction using this potassium β-aminoethyltrifluoroborate with bromo-heterocycles requires RuPhos as the phosphine ligand for a better yield of the targeted molecules (and even to furnish the desired product in some cases).[20]

Although, as discussed before, this β-aminoethylation reaction has been reported with simple unsubstituted 3-bromopyridine[20] and 4-bromopyridine,[18] no reports have appeared in the literature using 2-bromopyridines in similar routes. Also, to date no systematic study has been done for the synthesis of the pyridyl compounds related to structure **1**. Furthermore, this motif is particularly absent from commercial availability, and only a few syntheses have been reported for the simple 2-(2-aminoethyl)pyridines.[8a,21] Noteworthy, compared to related 3- or 4-halopyridine analogues, many palladium-catalyzed reactions do not work well with 2-halopyridines. One reason for this poor reactivity has been explained by the propensity of *ortho*-palladated pyridine complex **2** to undergo formation of more stable dimeric complex **3**, effectively removing the palladium from the catalytic cycle (Fig. 3).[22]

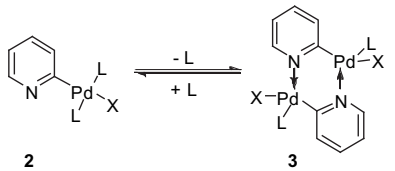
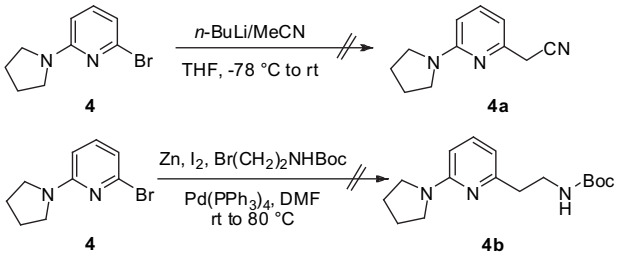


Figure 3. Dimerization of (2-pyridyl)palladium complexes.

2. Results and discussion

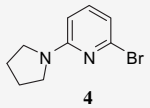
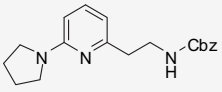
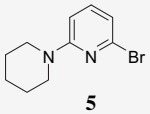
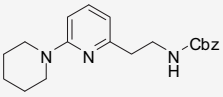
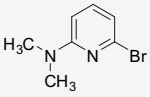
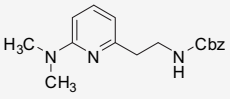
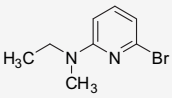
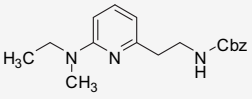
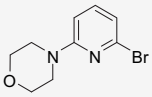
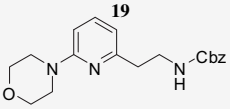
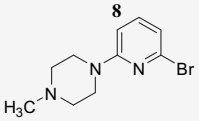
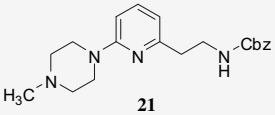
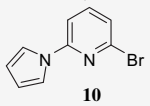
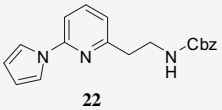
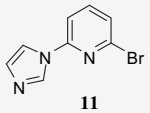
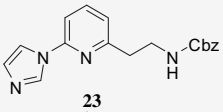
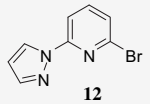
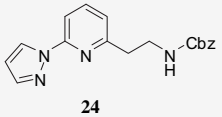
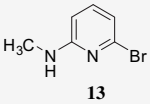
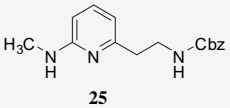
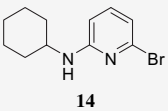
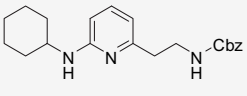
Since a wide variety of 2-bromopyridines bearing a 6-amino functionality are commercially available, we initially considered a *direct* approach using these as starting materials. Our initial approach involved the conversion of the 2-bromopyridine **4** into the cyanomethyl derivative **4a** using an alpha-lithiated acetonitrile[10] followed by the reduction of the nitrile functionality (Scheme 1). Unfortunately, our initial attempts to achieve this direct coupling with cyanomethyl organolithium and **4** were unsuccessful in providing the desired arylated acetonitrile **4a** in appreciable amounts. We then turned our attention from classical anion chemistry to the modern palladium-catalyzed reactions in order to achieve a direct synthesis of this scaffold. Toward this direction, we attempted the direct installation of *N*-Boc-protected aminoethyl functionality by preparing the zincate of *tert*-butyl 2-bromoethylcarbamate, hoping to prepare **4b** by inducing a Negishi-type coupling with **4** (Scheme 1).[14a] However, this palladium-mediated coupling procedure was unsuccessful in our hands.



Scheme 1. Unsuccessful initial approaches.

Next, we focused our attention on the palladium catalyzed Suzuki–Miyaura reactions reported by Corey–Roberts and Kamatani–Overman.[17,18] According to the Kamatani–Overman procedure, we first treated benzyl vinylcarbamate (**15**) with 9-BBN followed by aqueous NaOH to generate the organoborane species, which was subsequently reacted with compound **4** in the presence of $PdCl_2$(dppf) at room-temperature.[18] However, only small amounts (<10%) of desired product **16** were isolated in our initial attempts. We then followed the Suzuki–Miyaura modifications reported by Keen and co-workers for the tetrahydropyridoazepine system.[23] Using these conditions treatment of 2-bromopyridine with **15** and 9-BBN in the presence of $Pd(OAc)_2$, dppf, and K_2CO_3 at 65 °C did not

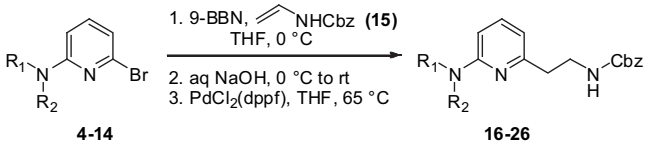
Table 1
Cross-coupling reactions of benzyl vinylcarbamate-derived boronates with various 6-bromo-2-aminopyridines

Entry	Bromopyridine	2-Aminoethyl Product	Yield[a] (%)
1	 **4**	 **16**	93
2	 **5**	 **17**	94
3	 **6**	 **18**	91
4	 **7**	 **19**	90
5	 **8**	 **20**	81
6	 **9**	 **21**	84
7	 **10**	 **22**	88[b]
8	 **11**	 **23**	75
9	 **12**	 **24**	77
10	 **13**	 **25**	72
11	 **14**	 **26**	76

[a] Reactions were carried out on 2 mmol scale.
[b] Reaction was carried out on 1 mmol scale.

furnish any appreciable amount of desired product. Also, the use of $PdCl_2$(dppf) as the catalyst instead of the $Pd(OAc)_2$ and dppf combination in the previous case was unsuccessful. Switching back to the hydroxide base (NaOH) and heating the reaction mixture of organoborane and **4** with catalytic $PdCl_2$(dppf) at 45 °C were found to be beneficial as the desired product **16** was observed to form in appreciable amounts (>50%). Towards this direction, heating the reaction mixture at 65 °C using the previous conditions provided the complete consumption of starting material **4**. A simplified work-up procedure was carried out to isolate the crude product which was subsequently purified to furnish the desired product in excellent yield (Table 1, entry 1). We also screened four other Pd-catalysts for the reaction of bromopyridine **4** under the same reaction conditions. Among these, $Pd(PPh_3)_4$ and $PdCl_2(PPh_3)_2$ were found to be useful for this reaction; the desired product **16** was formed in 63% and 68% yields, respectively. In contrast, $Pd_2(dba)_3$ and $Pd(dba)_2$ were ineffective for this transformation and only a small amount of the desired product **16** was observed in each case. Herein, we are pleased to report the synthesis of a novel series of aminopyridines in which the distal primary amine is protected as a benzyl carbamate moiety.

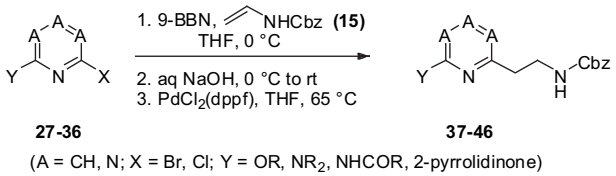
High yields of the desired products **16**–**26** were obtained from the corresponding 6-substituted-2-bromopyridine precursors **4**–**14**, using the previously described conditions (Scheme 2, Table 1). Notably, 2-bromo-6-morpholinopyridine (**8**) and 2-bromo-6-(*N*-methyl)piperazinopyridine (**9**) furnished the corresponding products **20** and **21** in high yields (entries 5 and 6). Relatively lower yields were obtained in the reactions with 2-bromo-6-imidazolopyridine (**11**) and 2-bromo-6-pyrazolopyridine (**12**) as the corresponding Cbz-protected (2-aminoethyl)pyridines **23** and **24** were formed in 75% and 77% yields, respectively (entries 8 and 9). To our delight, the monosubstituted precursors **13** and **14** also participated in the reaction to furnish the desired products **25** and **26**, respectively (entries 10 and 11), albeit in moderate yields, but obviating the need for an additional protection scheme.



Scheme 2. 9-BBN-mediated cross-coupling reaction of benzyl *N*-vinylcarbamate with 2-bromopyridines **4**–**14**.

We then applied our method to the preparation of (2-aminoethyl)pyridines **37**–**39** bearing an amido (or lactam) functionality and **40**–**42** bearing ether moieties at the pyridine C-6 position (Scheme 3, Table 2).

For all these amides (entries 1–3) and ethers (entries 4–6), the desired products **37**–**42** were obtained in high yields. Extension of this procedure to the related bromopyrazine precursor **33** (entry 7) and bromopyrimidine **34** (entry 8) afforded the desired products **43** and **44** in excellent yields. Most importantly, chlorides **35** and **36** afforded the targeted products **45** and **46**, respectively, albeit in moderate isolated yields (entries 9 and 10). To the best of our knowledge, this is the first example of a heteroaryl chloride participating in a β-aminoethylation reaction.



Scheme 3. 9-BBN-mediated cross-coupling reaction of benzyl *N*-vinylcarbamate with heteroaryl halides related to **4**.

In summary, a novel series of *N*-Cbz-protected (2-amino)-6-(2-aminoethyl)pyridines has been efficiently prepared from the corresponding heterocyclic bromides. We also extended this procedure to the 6-amido and 6-alkoxy variants as well as related pyrazine and pyrimidine derivatives and also demonstrated the use of heteroaryl chlorides for the first time in this reaction. These results should permit easy access to similar heterocyclic systems.

3. Experimental

3.1. General

^1H and ^{13}C NMR spectra were recorded on a Bruker UltraShield 300 or 400 MHz FT-NMR spectrometer. Chemical shifts (δ) are reported in parts per million (ppm). All coupling constants (J values) are reported in Hertz (Hz). Melting points were determined with a Mel-Temp electrothermal apparatus and are uncorrected. Low resolution mass spectra were recorded on a PE Sciex API 150EX mass spectrometer equipped with a Turbo Ionspray interface. High resolution mass spectra were obtained on a Waters MicroMass Q-TOF spectrometer. Pyridine starting materials were purchased from either Combi-Blocks or CombiPhos (except **28**, **29**, **32**, and **35** were purchased from Tyger Scientific, Milestone PharmTech, TCI America and HDH Pharma, respectively); benzyl vinylcarbamate was purchased from Organix; $PdCl_2$(dppf), 9-BBN (0.5 M solution in THF) and anhydrous THF were purchased from Aldrich and were used as received. All experiments were performed under a nitrogen atmosphere.

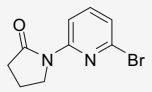
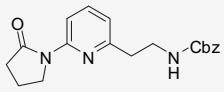
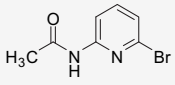
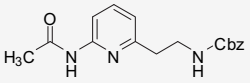
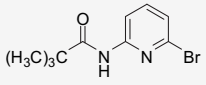
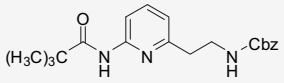
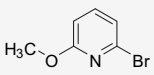
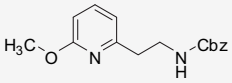
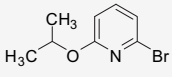
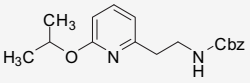
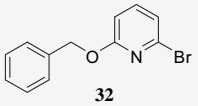
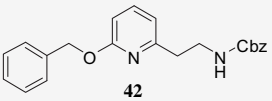
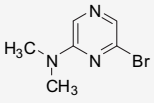
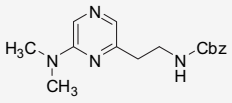
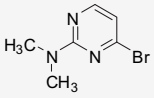
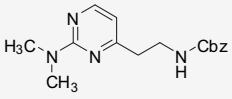
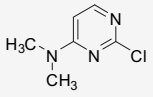
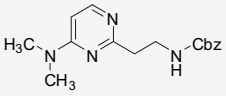
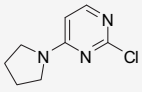
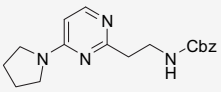
3.2. Representative experimental procedure

To a stirred solution of benzyl *N*-vinylcarbamate (**15**, 850 mg, 4.8 mmol) in anhydrous THF (6 mL) at 0 °C under nitrogen was added dropwise a solution of 9-borabicyclo[3.3.1]nonane (9-BBN, 0.5 M in THF, 8 mL), after which the mixture was warmed to room temperature, stirring for a total of 16 h. The mixture was then cooled to 0 °C and 3 M aqueous sodium hydroxide solution (3.6 mL) was slowly added dropwise. Stirring was continued for 30 min after which time the ice-bath was removed and the mixture was warmed to room temperature, stirring for a total of 2 h. The resulting reaction mixture was transferred into a mixture of the 2-amino-6-bromopyridine starting material (2 mmol) and $PdCl_2$(dppf) (146 mg, 0.2 mmol) in THF (10 mL) at room temperature under nitrogen, and the resulting mixture was degassed by bubbling nitrogen through the reaction mixture for 15 min. The mixture was then heated to 65 °C to stir for 24 h. The cooled mixture was diluted with saturated aqueous sodium bicarbonate solution (75 mL) and then extracted with ethyl acetate (3×100 mL). The combined organic extracts were dried over sodium sulfate, vacuum filtered through Hyflo and the filtrate solvents were removed under reduced pressure. The residue was purified by Teledyne-Isco CombiFlash Companion on silica gel to provide the desired product.

*3.2.1. Benzyl 2-(6-(pyrrolidin-1-yl)pyridin-2-yl)ethyl carbamate (**16**).* Yield=605 mg (93%), light yellow oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.33–7.28 (m, 6H), 6.60 (br s, 1H), 6.33 (d, 1H, J=7.2 Hz), 6.17 (d, 1H, J=8.4 Hz), 5.09 (s, 2H), 3.56 (q, 2H, J=5.7 Hz), 3.41 (t, 4H, J=6.4 Hz), 2.79 (t, 2H, J=5.9 Hz), 1.96–1.93 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.1, 156.8, 156.5, 137.5, 137.1, 128.5, 127.9, 127.8, 110.3, 104.2, 66.3, 46.6, 40.5, 36.4, 25.5; LRMS (ESI^+) m/z 326 $[M+H]^+$; HRMS (ESI^+) calcd for $C_{19}H_{24}N_3O_2$ [M+H]: 326.1869, found 326.1854.

*3.2.2. Benzyl 2-(6-(piperidin-1-yl)pyridin-2-yl)ethylcarbamate (**17**).* Yield=638 mg (94%), light yellow oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.35–7.28 (m, 6H), 6.46 (d, 1H, J=8.5 Hz), 6.38 (d, 1H, J=7.2 Hz), 5.97

Table 2
Cross-coupling reactions of benzyl vinylcarbamate-derived boronates with representative 2-halopyridines and related compounds

Entry	Bromopyridine	2-Aminoethyl Product	Yield[a] (%)
1	 **27**	 **37**	86
2	 **28**	 **38**	76
3	 **29**	 **39**	91
4	 **30**	 **40**	90
5	 **31**	 **41**	92
6	 **32**	 **42**	85[b]
7	 **33**	 **43**	91
8	 **34**	 **44**	82
9	 **35**	 **45**	53
10	 **36**	 **46**	56

[a] Reactions were carried out on 1 mmol scale.
[b] Reaction was carried out on 2 mmol scale.

(br s, 1H), 5.07 (s, 2H), 3.56 (q, 2H, *J*=6.0 Hz), 3.49–3.48 (m, 4H), 2.79 (t, 2H, *J*=6.1 Hz), 1.59 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.3, 157.5, 156.5, 138.0, 136.9, 128.5, 127.9, 127.5, 127.0, 111.7, 104.9, 66.4, 46.3, 40.3, 36.9, 25.5, 24.8; LRMS (ESI$^+$) *m*/*z* 340 [M+H]$^+$, HRMS (ESI$^+$) calcd for $C_{20}H_{26}N_3O_2$ [M+H]: 340.2025, found 340.2029.

*3.2.3. Benzyl 2-(6-(dimethylamino)pyridin-2-yl)ethylcarbamate (**18**).* Yield=545 mg (91%), colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37–7.28 (m, 6H), 6.38–6.34 (m, 2H), 6.11 (br s, 1H), 5.09 (s, 2H), 3.59 (q, 2H, *J*=5.9 Hz), 3.05 (s, 6H), 2.82 (t, 2H, *J*=6.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.0, 157.6, 156.6, 137.8, 137.1, 128.5, 128.0, 127.0, 110.8, 103.7, 66.4, 40.4, 38.2, 36.8; LRMS (ESI$^+$) *m*/*z* 300 [M+H]$^+$; HRMS (ESI$^+$) calcd for $C_{17}H_{22}N_3O_2$ [M+H]: 300.1712, found 300.1713.

*3.2.4. Benzyl 2-(6-(ethyl(methyl)amino)pyridin-2-yl)ethylcarbamate (**19**).* Yield=564 mg (90%), light yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34–7.29 (m, 6H), 6.32 (t, 2H, *J*=7.8 Hz), 6.16 (br s, 1H), 5.09 (s, 2H), 3.58–3.50 (m, 4H), 2.98 (s, 3H), 2.79 (t, 2H, *J*=6.0 Hz), 1.10 (t, 3H, *J*=7.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.0, 157.7, 156.5, 137.7, 137.0, 128.5, 127.9, 127.0, 110.5, 103.4, 66.4, 44.6, 40.3, 36.8, 35.5, 11.9; LRMS (ESI$^+$) *m*/*z* 314 [M+H]$^+$; HRMS (ESI$^+$) calcd for $C_{18}H_{24}N_3O_2$ [M+H]: 314.1869, found 314.1873.

*3.2.5. Benzyl 2-(6-morpholinopyridin-2-yl)ethylcarbamate (**20**).* Yield=551 mg (81%), colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42–7.29 (m, 6H), 6.51–6.45 (m, 2H), 5.80 (br s, 1H), 5.08 (s, 2H), 3.76 (t, 4H, *J*=4.7 Hz), 3.57 (q, 2H, *J*=6.0 Hz), 3.45 (t, 4H, *J*=4.9 Hz), 2.83 (t, 2H, *J*=6.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.2, 157.6, 156.4, 138.2, 136.8, 128.5, 128.1, 113.2, 104. 7, 66.7, 66.5, 45.6, 40.2, 37.0; LRMS (ESI$^+$) *m*/*z* 342 [M+H]$^+$; HRMS (ESI$^+$) calcd for $C_{19}H_{24}N_3O_3$ [M+H]: 342.1818, found 342.1820.

*3.2.6. Benzyl 2-(6-(4-methylpiperazin-1-yl)pyridin-2-yl)ethylcarbamate (**21**).* Yield=595 mg (84%), light brown oil: ^{1}H NMR ($CDCl_3$,

300 MHz) δ 7.40–7.30 (m, 6H), 6.46 (t, 2H, J=7.1 Hz), 5.92 (br s, 1H), 5.08 (s, 2H), 3.60–3.50 (m, 6H), 2.82 (t, 2H, J=6.2 Hz), 2.45 (t, 4H, J=4.9 Hz), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.0, 157.6, 156.4, 138.1, 136.9, 128.5, 128.0, 127.9, 112.6, 104.8, 66.5, 54.9, 46.2, 45.2, 40.2, 36.9; LRMS (ESI$^+$) m/z 355 [M+H]$^+$; HRMS (ESI$^+$) calcd for $C_{20}H_{27}N_4O_2$ [M+H]: 355.2134, found 355.2122.

*3.2.7. Benzyl 2-(6-(1H-pyrrol-1-yl)pyridin-2-yl)ethylcarbamate (**22**).* Yield=282 mg (88%), light yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.57 (t, 1H, J=7.9 Hz), 7.48 (t, 2H, J=2.3 Hz), 7.32–7.28 (m, 5H), 7.09 (d, 1H, J=8.2 Hz), 6.88 (d, 1H, J=7.4 Hz), 6.32 (t, 2H, J=2.3 Hz), 5.46 (br s, 1H), 5.07 (s, 2H), 3.63 (q, 2H, J=6.1 Hz), 2.94 (t, 2H, J=6.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.6, 156.4, 150.8, 139.0, 136.7, 128.5, 128.0, 119.7, 118.0, 111.3, 109.0, 66.6, 40.0, 37.1; LRMS (ESI$^+$) m/z 322 [M+H]$^+$; HRMS (ESI$^+$) calcd for $C_{19}H_{20}N_3O_2$ [M+H]: 322.1556, found 322.1562.

*3.2.8. Benzyl 2-(6-(1H-imidazol-1-yl)pyridin-2-yl)ethylcarbamate (**23**).* Yield=481 mg (75%), light yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.29 (s, 1H), 7.68 (t, 1H, J=7.8 Hz), 7.61 (s, 1H), 7.32–7.27 (m, 5H), 7.15–7.14 (m, 2H), 7.06 (d, 1H, J=7.5 Hz), 5.59 (br s, 1H), 5.08 (s, 2H), 3.65 (q, 2H, J=6.2 Hz), 3.01 (t, 2H, J=6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.3, 156.4, 148.5, 139.4, 136.6, 134.8, 130.5, 128.5, 128.0, 121.6, 116.1, 109.9, 66.5, 39.9, 37.3; LRMS (ESI$^+$) m/z 323 [M+H]$^+$; HRMS (ESI$^+$) calcd for $C_{18}H_{19}N_4O_2$ [M+H]: 323.1508, found 323.1513.

*3.2.9. Benzyl 2-(6-(1H-pyrazol-1-yl)pyridin-2-yl)ethylcarbamate (**24**).* Yield=495 mg (77%), light yellow solid: mp 44–46 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.53 (dd, 1H, J=2.6 Hz, 0.5 Hz), 7.81 (d, 1H, J=8.0 Hz), 7.72–7.66 (m, 2H), 7.35–7.30 (m, 6H), 7.00 (d, 1H, J=7.4 Hz), 6.43–6.41 (m, 1H), 5.33 (br s, 1H), 5.09 (s, 2H), 3.67 (q, 2H, J=6.2 Hz), 2.99 (t, 2H, J=6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.0, 156.5, 151.2, 142.1, 139.3, 136.7, 128.6, 128.2, 127.0, 121.1, 110.2, 107.8, 66.7, 40.1, 37.2; LRMS (ESI$^+$) m/z 323 [M+H]$^+$; HRMS (ESI$^+$) calcd for $C_{18}H_{19}N_4O_2$ [M+H]: 323.1508, found 323.1516.

*3.2.10. Benzyl 2-(6-(methylamino)pyridin-2-yl)ethylcarbamate (**25**).* Yield=409 mg (72%), light yellow solid: mp 82–84 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33–7.28 (m, 6H), 6.40 (d, 1H, J=7.2 Hz), 6.20 (d, 1H, J=8.3 Hz), 5.90 (br s, 1H), 5.08 (s, 2H), 4.60 (br s, 1H), 3.55 (q, 2H, J=6.0 Hz), 2.85 (d, 3H, J=5.2 Hz), 2.78 (t, 2H, J=6.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.3, 157.9, 156.5, 138.0, 136.9, 128.5, 128.1, 128.0, 112.1, 103.9, 66.5, 40.4, 37.0, 29.1; LRMS (ESI$^+$) m/z 286 [M+H]$^+$; HRMS (ESI$^+$) calcd for $C_{16}H_{20}N_3O_2$ [M+H]: 286.1556, found 286.1546.

*3.2.11. Benzyl 2-(6-(cyclohexylamino)pyridin-2-yl)ethylcarbamate (**26**).* Yield=537 mg (76%), light brown oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35–7.25 (m, 6H), 6.35 (d, 1H, J=7.2 Hz), 6.18 (d, 1H, J=8.3 Hz), 5.90 (br s, 1H), 5.09 (s, 2H), 4.40 (d, 1H, J=6.4 Hz), 3.58–3.48 (m, 3H), 2.77 (t, 2H, J=6.1 Hz), 2.02–1.98 (m, 2H), 1.72–1.68 (m, 2H), 1.60–1.56 (m, 1H), 1.39–1.10 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.1, 157.8, 156.5, 137.9, 137.0, 128.5, 128.2, 128.1, 111.7, 104.8, 66.6, 50.4, 40.5, 37.0, 33.5, 25.9, 25.0; LRMS (ESI$^+$) m/z 354 [M+H]$^+$; HRMS (ESI$^+$) calcd for $C_{21}H_{28}N_3O_2$ [M+H]: 354.2182, found 354.2182.

*3.2.12. Benzyl 2-(6-(2-oxopyrrolidin-1-yl)pyridin-2-yl)ethylcarbamate (**37**).* Yield=292 mg (86%), off-white solid: mp 85–87 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.22 (d, 1H, J=8.4 Hz), 7.57 (t, 1H, J=7.9 Hz), 7.32–7.27 (m, 5H), 6.86 (d, 1H, J=7.3 Hz), 5.74 (br s, 1H), 5.08 (s, 2H), 4.05 (t, 2H, J=7.1 Hz), 3.60 (q, 2H, J=5.9 Hz), 2.91 (t, 2H, J=6.1 Hz), 2.61 (t, 2H, J=8.1 Hz), 2.07–2.00 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.9, 157.2, 156.4, 151.3, 138.1, 136.8, 128.5, 128.0, 118.8, 112.2, 66.5, 47.3, 40.0, 36.8, 33.6, 17.5; LRMS (ESI$^+$) m/z 340 [M+H]$^+$; HRMS (ESI$^+$) calcd for $C_{19}H_{22}N_3O_3$ [M+H]: 340.1661, found 340.1657.

*3.2.13. Benzyl 2-(6-acetamidopyridin-2-yl)ethylcarbamate (**38**).* Yield=239 mg (76%), off-white solid: mp 86–88 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.21 (br s, 1H), 8.02 (d, 1H, J=7.8 Hz), 7.57 (t, 1H, J=7.9 Hz), 7.32 (s, 5H), 6.84 (d, 1H, J=7.4 Hz), 5.34 (br s, 1H), 5.16–5.08 (m, 2H), 3.56 (q, 2H, J=6.2 Hz), 2.86 (t, 2H, J=6.5 Hz), 2.17 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.9, 157.6, 156.5, 151.1, 138.9, 136.7, 128.6. 128.2, 119.3, 111.6, 66.7, 40.2, 37.4, 24.7; LRMS (ESI$^+$) m/z 314 [M+H]$^+$; HRMS (ESI$^+$) calcd for $C_{17}H_{20}N_3O_3$ [M+H]: 314.1505, found 314.1494.

*3.2.14. Benzyl 2-(6-pivalamidopyridin-2-yl)ethylcarbamate (**39**).* Yield=324 mg (91%), colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.08 (d, 1H, J=8.3 Hz), 7.98 (br s, 1H), 7.58 (t, 1H, J=7.9 Hz), 7.32–7.29 (m, 5H), 6.86 (d, 1H, J=7.4 Hz), 5.25 (br s, 1H), 5.08 (s, 2H), 3.57 (q, 2H, J=6.3 Hz), 2.88 (t, 2H, J=6.5 Hz), 1.31 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.1, 157.4, 156.4, 151.2, 138.9, 136.7, 128.6, 128.1, 119.2, 111.7, 66.7, 40.3, 39.8, 37.4, 27.5; LRMS (ESI$^+$) m/z 356 [M+H]$^+$; HRMS (ESI$^+$) calcd for $C_{20}H_{26}N_3O_3$ [M+H]: 356.1974, found 356.1972.

*3.2.15. Benzyl 2-(6-methoxypyridin-2-yl)ethylcarbamate (**40**).* Yield=258 mg (90%), colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.46–7.41 (m, 1H), 7.31–7.26 (m, 5H), 6.67 (d, 1H, J=7.2 Hz), 6.56 (d, 1H, J=8.3 Hz), 5.67 (br s, 1H), 5.08 (s, 2H), 3.88 (s, 3H), 3.59 (q, 2H, J=6.1 Hz), 2.87 (t, 2H, J=6.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.7, 157.0, 156.4, 139.0, 136.8, 128.5, 128.0, 115.9, 108.3, 66.5, 53.2, 40.2, 36.8; LRMS (ESI$^+$) m/z 287 [M+H]$^+$; HRMS (ESI$^+$) calcd for $C_{16}H_{19}N_2O_3$ [M+H]: 287.1396, found 287.1395.

*3.2.16. Benzyl 2-(6-isopropoxypyridin-2-yl)ethylcarbamate (**41**).* Yield=290 mg (92%), light yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45–7.41 (m, 1H), 7.34–7.29 (m, 5H), 6.64 (d, 1H, J=7.2 Hz), 6.51 (d, 1H, J=8.3 Hz), 5.66 (br s, 1H), 5.27–5.22 (m, 1H), 5.09 (s, 2H), 3.59 (q, 2H, J=6.0 Hz), 2.86 (t, 2H, J=6.2 Hz), 1.31 (d, 6H, J=6.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.1, 157.0, 156.5, 139.1, 136.9, 128.5, 128.1, 115.5, 109.2, 67.9, 66.6, 40.3, 36.9, 22.1; LRMS (ESI$^+$) m/z 315 [M+H]$^+$; HRMS (ESI$^+$) calcd for $C_{18}H_{23}N_2O_3$ [M+H]: 315.1709, found 315.1703.

*3.2.17. Benzyl 2-(6-(benzyloxy)pyridin-2-yl)ethylcarbamate (**42**).* Yield=614 mg (85%), colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.48–7.25 (m, 11H), 6.69–6.62 (m, 2H), 5.44 (br s, 1H), 5.34 (s, 2H), 5.07 (s, 2H), 3.58 (q, 2H, J=6.1 Hz), 2.87 (t, 2H, J=6.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.2, 156.9, 156.4, 139.2, 137.5, 136.8, 128.5, 128.1, 127.8, 116.3, 108.9, 67.5, 66.6, 40.1, 36.9; LRMS (ESI$^+$) m/z 363 [M+H]$^+$; HRMS (ESI$^+$) calcd for $C_{22}H_{23}N_2O_3$ [M+H]: 363.1709, found 363.1701.

*3.2.18. Benzyl 2-(6-(dimethylamino)pyrazin-2-yl)ethylcarbamate (**43**).* Yield=273 mg (91%), light brown oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.84 (s, 1H), 7.64 (s, 1H), 7.32–7.30 (m, 5H), 5.69 (br s, 1H), 5.09 (s, 2H), 3.59 (q, 2H, J=6.1 Hz), 3.07 (s, 6H), 2.81 (t, 2H, J=6.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.4, 154.2, 151.4, 136.8, 130.8, 128.5, 128.0, 127.7, 66.5, 39.9, 37.5, 34.3; LRMS (ESI$^+$) m/z 301 [M+H]$^+$; HRMS (ESI$^+$) calcd for $C_{16}H_{21}N_4O_2$ [M+H]: 301.1665, found 301.1663.

*3.2.19. Benzyl 2-(2-(dimethylamino)pyrimidin-4-yl)ethylcarbamate (**44**).* Yield=246 mg (82%), off-white solid: mp 93–95 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.08 (d, 1H, J=6.2 Hz), 7.34–7.28 (m, 5H), 6.25 (d, 1H, J=6.2 Hz), 5.91 (br s, 1H), 5.09 (s, 2H), 3.65 (q, 2H, J=5.9 Hz), 3.07 (s, 6H), 2.95 (t, 2H, J=6.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.8, 161.9, 156.4, 155.2, 137.0, 128.5, 128.1,

128.0, 100.3, 66.5, 39.0, 38.5, 37.0; LRMS (ESI^+) m/z 301 $[M+H]^+$; HRMS (ESI^+) calcd for $C_{16}H_{21}N_4O_2$ [M+H]: 301.1665, found 301.1667.

*3.2.20. Benzyl 2-(4-(dimethylamino)pyrimidin-2-yl)ethylcarbamate (**45**).* Yield=160 mg (53%), light brown solid: mp 95–97 °C; ^1H NMR (DMSO-d_6, 300 MHz) δ 8.07 (d, 1H, J=6.2 Hz), 7.39–7.23 (m, 6H), 6.47 (d, 1H, J=6.2 Hz), 5.01 (s, 2H), 3.45–3.35 (m, 2H), 3.03 (s, 6H), 2.78 (t, 2H, J=7.4 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 166.6, 161.5, 156.0, 155.0, 137.2, 128.3, 127.7, 127.6, 100.4, 65.1, 36.4; LRMS (ESI^+) m/z 301 $[M+H]^+$; HRMS (ESI^+) calcd for $C_{16}H_{21}N_4O_2$ [M+H]: 301.1665, found 301.1659.

*3.2.21. Benzyl 2-(4-(pyrrolidin-1-yl)pyrimidin-2-yl)ethylcarbamate (**46**).* Yield=182 mg (56%), light brown solid: mp 105–107 °C; ^1H NMR (DMSO-d_6, 400 MHz) δ 8.05 (d, 1H, J=6.0 Hz), 7.38–7.24 (m, 6H), 6.28 (d, 1H, J=6.1 Hz), 5.01 (s, 2H), 3.43–3.34 (m, 6H), 2.77 (t, 2H, J=7.4 Hz), 1.93–1.88 (m, 4H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 166.9, 159.3, 156.0, 154.5, 137.2, 128.3, 127.7, 127.6, 101.4, 65.1, 45.8; LRMS (ESI^+) m/z 327 $[M+H]^+$; HRMS (ESI^+) calcd for $C_{18}H_{23}N_4O_2$ [M+H]: 327.1821, found 327.1825.

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Supplementary data

^1H and ^{13}C NMR spectra of all compounds prepared. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2010.01.025.

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