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Microwave-Assisted Synthesis of Novel (5-Nitropyridin-2-yl)alkyl and (5-Nitropyridin-3-yl)alkyl Carbamates

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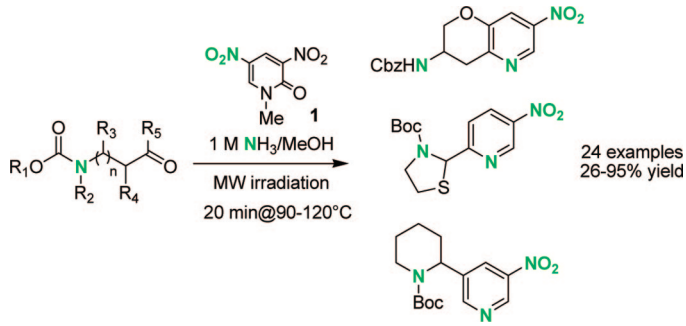

A straightforward approach to novel (5-nitropyridin-2-yl)alkyl and (5-nitropyridin-3-yl)alkyl carbamate building blocks is presented in this study. Their construction is achieved by condensation of *N*-carbamate α- and *β*-amino carbonyl derivatives with 1-methyl-3,5-dinitro-2-pyridone **1** under microwave irradiation. Judiciously chosen modifications in the nature of the parent carbonyl starting material has influenced the regiochemical outcome of the reaction and allowed an efficient access to novel nitrogen-containing scaffolds. Compounds sharing morphological similarities have been gathered in three libraries differing from each other in a single structural parameter.

Introduction

Bioactive structures incorporating a 3-aminopyridine motif constitute a significant class of pharmaceutical compounds, and to date, nearly 100 marketed and developmental pharmaceutics featuring this pattern have been reported.[1] They cover a broad spectrum of activity and include, for instance, promising cytotoxic anticancer therapeutics,[2] potent angiotensin-receptor antagonists,[3] and histamine-receptor antagonists.[4] The *β*-aminopyridine core can also be considered as a subunit of more complex nitrogen-containing polycyclic systems commonly known as *β*-carbolines. These pyrido[3,4-*b*]indoles are substructures found in some interesting natural products with biological and pharmaceutical importance like the well-known manzamine-related alkaloids,[5] the recently isolated shishijimicins,[6] or the eudistomins.[7]

Chemical entities possessing a *β*-aminopyridine core structure are in themselves attractive building blocks that are challenging

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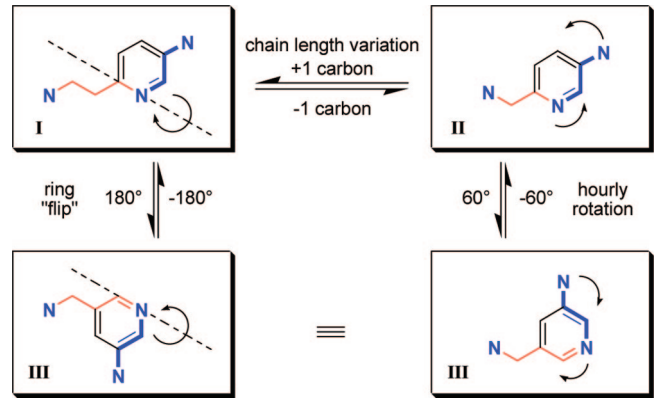
to build. Very few examples in the literature report protocols for the direct β-nitration of preformed pyridine rings.[8a−d] While the inductive effect of the nitrogen atom allows both the α- and γ-activations in nucleophilic substitution, pyridine undergoes electrophilic substitution reactions at the nitrogen atom and at the β-position. However, it is also a π-deficient heterocycle and its electronic profile tends to neutralize the C-3 carbon, which is hard to attack without the assistance of additional activating substituents connected to the ring.[8e] Recently, Katritzky and co-workers reported a remarkable preparation of β-nitropyridines using the system nitric acid/trifluoroacetic anhydride.[8f] Nevertheless, the nitration steps remain somewhat difficult or unpleasant to carry out, and the yields drop dramatically with increasing molecular complexity. In addition, nitrations occur in strongly acidic media, which are often incompatible with sensitive functional groups. An alternative approach addressing this issue and circumventing the troublesome nitration step would be to construct the pyridine core by condensing an intermediate bearing a nitro group with suitable carbonyl compounds in the presence of ammonia. Among the reagents typically used for this type of cyclization are the nitro-vinamidinium salts developed by Merck[9a,b] and the 3,5-dinitro-1-methyl-2-pyridone **1** reported by Tohda.[10] Although the latter developed a rapid and powerful method to access β-nitropyridines, few examples of its application in organic synthesis have been disclosed in the literature to date. In addition, the scope of this reaction has been mostly limited to cyclic symmetrical ketones.[11a−h]

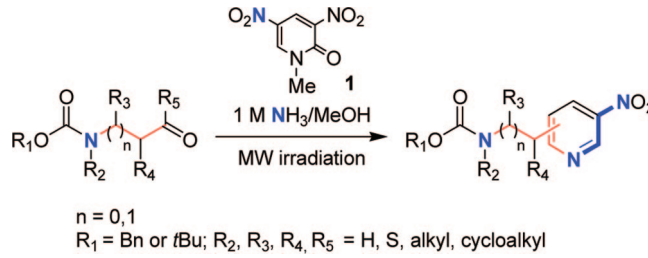
In connection with a medicinal chemistry program, we became interested in elaborating novel pyridine-based chemotypes presenting a rigidified arrangement between two nitrogen atoms and allowing fine-tuning of the position of a third nitrogen via a carbon spacer. They can be organized into three generic families of compounds **I**, **II**, and **III** that possess close topology and differ from each other in a sole parameter. Hence, the spatial display of the three key atoms would be directly related either by a 180° "flip" of the heterocyclic ring, a variation of one carbon in the chain length, or by a 60° hourly rotation of the two nitrogen atoms incorporated in the core structure (Scheme 1).

Therefore, we envisaged to construct molecular templates derived from a β-nitropyridine unit fused with an additional carbon frame bearing a carbamate group. In addition, the selection of both a nitro group and a carbamate group on the same molecule would circumvent any problem of orthogonal reactivity at a later point. Hence, our retrosynthetic plan led us

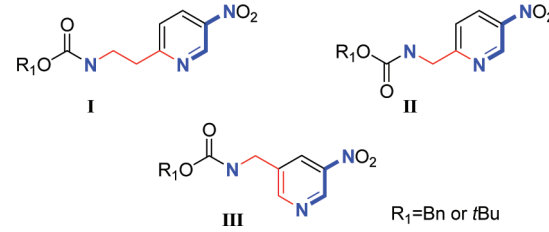
SCHEME 1



SCHEME 2



SCHEME 3



to condense the 3,5-dinitro-1-methyl-2-pyridone **1** with a variety of *N*-carbamate α- and β-amino carbonyls (Scheme 2).

The formation of the β-nitropyridine ring with **1** proceeds only with starting materials featuring at least one CH_2 motif flanking the carbonyl function. A plausible mechanism involves the abstraction of a first adjacent proton, leading to an enol species capable of reacting with a complex formed after addition of a molecule of ammonia to the pyridone system. Next, the departure of a second geminal proton is necessary for the formation of a cyclic enamine intermediate that finally rearomatizes to give the pyridine ring.[10] According to this mechanistic sequence, the nature of the *N*-carbamate α- and β-amino carbonyl will control the position of the additional nitrogen-containing skeleton branched to the β-nitropyridine. In this paper, we report our efforts in designing and preparing three collections of novel (5-nitropyridin-2-yl)alkyl carbamates **I** and **II** and (5-nitropyridin-3-yl)alkyl carbamates **III** using microwave synthesis (Scheme 3).

Results and Discussion

Most of the requisite carbonyl starting materials were not commercially accessible and had to be prepared. According to a classical procedure starting from commercially available carboxylic acids, methyl ketones **2a**−**d** and **3a**−**c** (Table 1, entries 1−7), **8a**, and **9a** (Table 3, entries 1 and 4) as well as aldehyde **6b** (Table 2, entry 2) were synthesized in good overall

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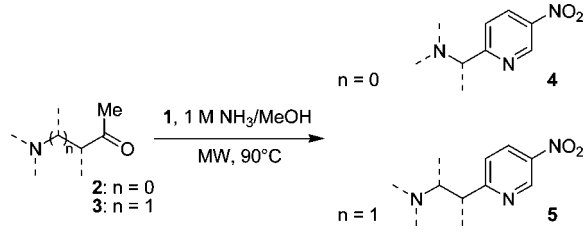
TABLE 1. Condensation of *N*-Carbamate α- and *β*-Amino Methyl Ketones 2 and 3 with 1



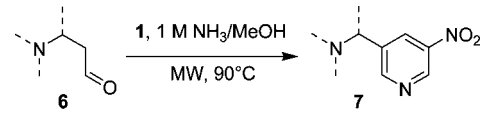
entry	carbonyl	product	group	yield [a] (%)
1	2a	4a	II	95
2	2b	4b	II	65
3	2c	4c	II	74
4	2d	4d	II	70
5	3a	5a	I	53
6	3b	5b	I	74
7	3c	5c	I	70

[a] Isolated yields.

yields via formation of the Weinreb amide followed by displacement with MeMgBr or reaction with DIBAL-H.[12a,b] The preparation of the cyclic intermediates **9b**, **9c**, and **9d** (Table 3, entries 5−7) involved aza-Michael addition of a benzyl carbamate group onto the *β*-position of an enone *π*-system. In many reports, this reaction proceeds smoothly when catalyzed by transition metal and metal salts such as $Bi(NO_3)_3$, $PtCl_4$, or $Cu(OTf)_2$.[13a−c] In our hands, $Bi(NO_3)_3$ turned out to be the most efficient reagent, providing us with the desired *N*-carbamate-*β*-cycloketones in good to excellent yields (Scheme 4). Access to aldehyde **6c** (Table 2, entry 3) was achieved by Dess−Martin periodinane oxidation of the corresponding primary alcohol.[14]

Acetyl carbamates **2**[15,16] and **3** should undergo the cyclization process and furnish only one regioisomer, namely, a (5-nitropyridin-2-yl)alkyl carbamate. The condensation of the pyridone **1** with the methyl ketone **2a** (Table 1, entry 1) was

TABLE 2. Condensation of *N*-Carbamate *β*-Amino Aldehydes 6 with 1



entry	carbonyl	product	group	yield [a] (%)
1	6a	7a	III	42
2	6b	7b	III	30[b]
3	6c	7c	III	40

[a] Isolated yields. [b] Aldehyde **6b** was used directly without any further purification in the condensation reaction, therefore yield for two steps.

initially chosen in order to define an optimal and general protocol.[17] When a mixture of **2a** and **1** was heated under conventional thermal conditions in the presence of NH_3 in methanol at 90 °C for 20 min, the nitropyridine **4a** was isolated in 37% yield. Longer reaction times or higher temperatures gave no significant improvement and, therefore, prompted us to explore the use of microwave technology.

Thus, when the same mixture was reacted at 90 °C for 20 min under microwave irradiation, the conversion was cleaner and a substantial increase in yield (95%) was noticed. To explore the substrate tolerance of this reaction, we extended the above methodology to several additional carbonyl substrates. As can be seen from the results summarized in Table 1, the products of condensation were readily prepared and furnished us with six structures from chemotypes **I** or **II**. Hence, good to excellent yields were obtained for either five-membered nitrogen-containing rings **4a**, **4b**, and **4d** (Table 1, entries 1, 2, and 4) or piperidine derivatives **4c** and **5b** (Table 1, entries 3 and 6).

By comparing the results for condensation of methyl ketones **2a** and **2b** with **1**, one can note that the presence of an additional heteroatom (Table 1, entry 2) on the carbonyl partner seems to affect slightly the rate of conversion. Interestingly, when the transformation was conducted with a substrate featuring an

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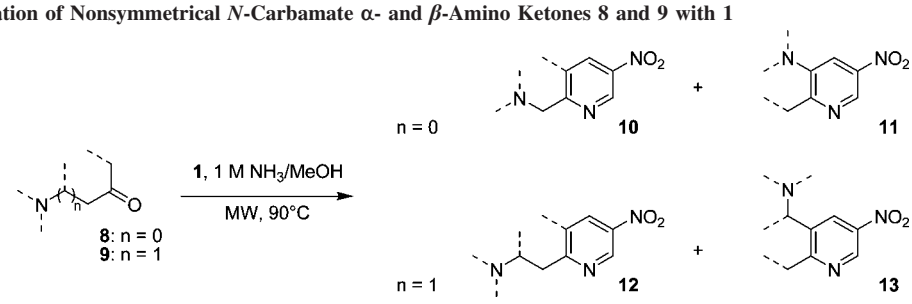
(17) As an initial study, we set out to investigate the role of reaction solvent. In addition to the solvent medium NH_3/MeOH, which was typically used in previous syntheses for this condensation, additional commercially available solutions were also tested as ammonia sources. Except for NH_3/EtOH, which furnished comparable results to those obtained in MeOH, reactions conducted in NH_3/*i*-propanol or in NH_3/dioxane resulted in the formation of only trace amounts of the desired *β*-nitropyridines. The low rate of conversion was mainly due to the poor solubility of **1**, and subsequent solvent combinations with CH_3CN, DMF, or pyridine did not significantly improve the condensation outcomes.

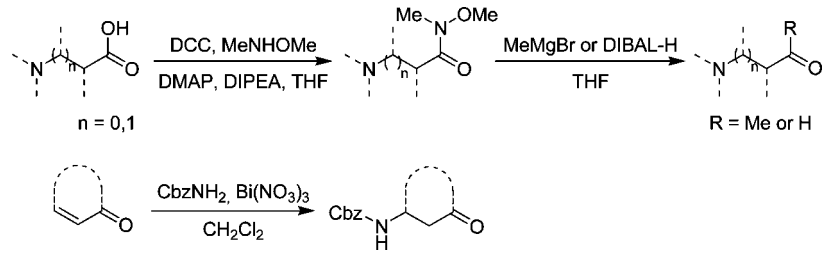
TABLE 3. Condensation of Nonsymmetrical *N*-Carbamate α- and *β*-Amino Ketones 8 and 9 with 1



entry	carbonyl	products	ratio	group	yield[a] (%)
1	**8a**	**10a** + **11a**	1/2.5	**II/-**	74
2	**8b**	**10b** + **11b**	99/1[b]	**II/-**	26
3	**8c**	**10c** + **11c**	3/1	**II/-**	30
4	**9a**	**12a** + **13a**	2/1	**I/III**	74
5	**9b**	**12b** + **13b**	2.5/1	**I/III**	52
6	**9c**	**12c** + **13c**	3/1	**I/III**	75
7	**9d**	**12d**[c] + **13d**	1/7.5	**I/III**	64

[a] Isolated yields. [b] Product **11b** detected but not isolated. [c] Obtained after condensation performed at 120 °C.

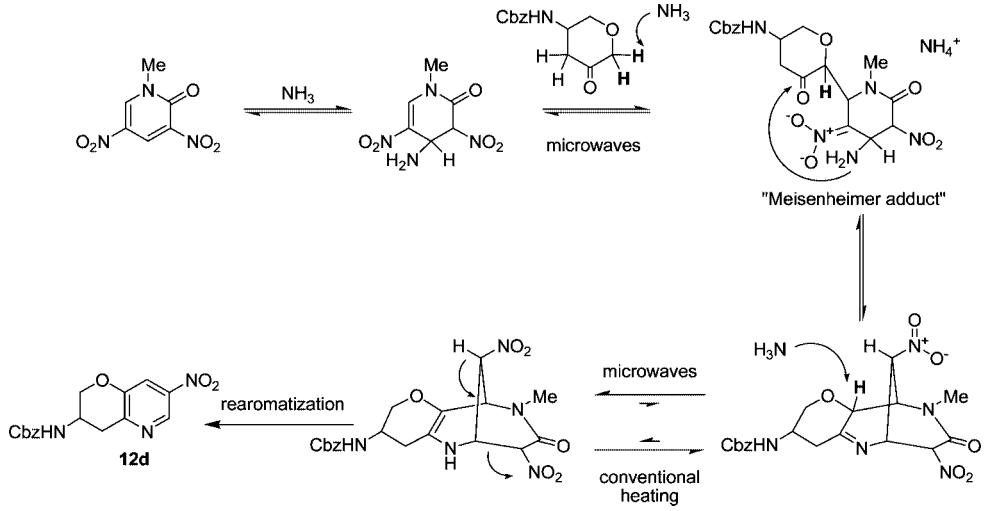
SCHEME 4



exocyclic nitrogen (Table 1, entry 4), the reaction furnished exclusively the desired product **5a**, but the yield did not exceed 53%.

We next undertook to react **1** with several *N*-carbamate *β*-amino aldehydes **6** enolizable only at the α-position to selectively prepare (5-nitropyridin-3-yl)alkyl carbamates. In contrast to the previously described methyl ketones depicted in Table 1, the condensation of **1** with aldehydes resulted in a structural permutation of the nitrogen-containing moiety from the 2-position to the 3-position to afford 3-alkyl-5-nitropyridines of type **III**. One of the drawbacks of using aldehydes is their relative instability and propensity for polymerization reactions. As summarized in Table 2, we were able to prepare three novel structures **7a**, **7b**, and **7c** in moderate yields. We thought that the microwave-assisted condensation would benefit from the thermal effect and

SCHEME 5. Proposed Mechanism for the Formation of 12d



prevent side reactions.[18] Despite variation of parameters such as reaction time or temperature, no significant improvement in term of yields could be obtained. In addition, direct transfer of energy to the solvent in sealed vessels competes with superheating, which might lead to the formation of undesired side products frequently encountered with aldehyde chemistry. Nevertheless, the low isolated yield observed for nitropyridine **7b** (Table 2, entry 2) can be probably attributed to the relative impurity of the aldehyde **6b**, which was used without any further purification after its preparation.[19]

Finally, we applied our procedure to nonsymmetrical ketones featuring two CH_2 motifs at both sides of the carbonyl function. According to the proposed mechanism previously discussed, we envisioned that nonsymmetrical starting materials should provide us with two different nitropyridine products. The condensation of pyridone **1** with the secondary carbamate **8a**[20] (Table 3, entry 1) was first examined. As expected, the two nitropyridine derivatives **10a** and **11a** were obtained in a good yield of 74% and in a ratio 1/2.5, respectively. Interestingly, this ratio was completely inverted with the cyclic counterpart **8c** (Table 3, entry 3), but the yield of isolated products **10c** and **11c** dropped to 30%. Surprisingly, when the condensation was carried out with pyrrolidin-3-one **8b** (Table 3, entry 2), the observed ratio for the two possible products was further shifted and only the desired nitropyridine derivative **10b** was isolated in a moderate yield. The second regioisomer **11b** could hardly be detected by TLC analysis and LC−MS spectroscopy. The two undesired products **11a** and **11c** were isolated and characterized. As predicted, each of the *N*-carbamate β-amino ketones **9a**−**c** (Table 3, entries 4−6)[13,21,22] afforded two structures of type **I** and **III** with excellent yields and with proportions ranging from 2/1 to 3/1. It is likely that the bulky Boc and Cbz protecting groups in the cyclic series interact with the substituents on the preformed pyridine ring and therefore account for the predominant formation of both **12b** and **12c**. The influence of the same steric factors reinforced by the deficit of one carbon can also be used to explain the similar regioselectivity observed for the pairs **10b/11b** and **10c/11c** (Table 3, entries 2 and 3). Furthermore, when comparing the overall yields obtained for endocyclic versus exocyclic nitrogen atoms, it is likely that the nitrogen atom of the α-amino ketones significantly impacts the acidity of the hydrogen atoms and therefore hinders the enol formation. One can also postulate that the results observed with the acyclic ketones **8a** and **9a** (Table 3, entries 1 and 4) could be explained by the formation of less rigid intermediates accompanied by reduced sensitivity to the internal geometry. All pairs of isomers could be separated by normal or reversed phase chromatography and were fully characterized. It is important to note that, while only one study reports the use of this methodology for the preparation of bicyclic structures featuring an intracyclic nitrogen atom starting from symmetric cycloketones,[11b] the preparation of β-nitropyridine systems from nonsymmetric cycloketones bearing an exocyclic nitrogen has not been previously reported.

Microwave-assisted chemistry has not only demonstrated a marked enhancement in terms of yield and short reaction times in organic synthesis but it also allows access to reaction products that are not attainable under classical heating conditions.[23,24] As an illustration, when the condensation was attempted with the ketone **9d** (Table 3, entry 7)[25] under classical heating, only the isomer **13d** was isolated in a low 18% yield. No trace of the second theoretical heterocycle **12d** was observed even at higher reaction temperatures.

The origin of the selectivity can be rationalized by the presence of the oxygen heteroatom that completely shuts down the deprotonation process at this side of the ketone group.

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(25) The preparation of **9d** started from the corresponding 2*H*-pyran-3(6*H*)-one, which had to be synthesized according to: Eiden, F.; Wanner, K. T. *Arch. Pharm.* **1985**, *318*, 548–555.

Nevertheless, we were pleased to observe that the same reaction sequence carried out under microwave irradiation at 120 °C for 10 min afforded a mixture of two β-nitropyridines **12d** and **13d** in a 64% yield, the ratio of 7.5/1 being favorable toward the isomer **13d**. On the basis of experimental observations, it is reasonable to imagine that the initial enol formation may occur to some extent to yield a Meisenheimer adduct in equilibrium with the imine form that failed to undergo the second proton abstraction under classical conditions (Scheme 5). It is likely that the different rate of heating and the higher reaction temperature under microwave conditions are responsible for the observed formation of the second oxygen-containing bicyclic system **12d**.

Conclusion

In conclusion, we have developed an efficient and reliable strategy for the microwave-assisted preparation of flexible or conformationally constrained amino scaffolds based on a β-nitropyridine subunit. The approach involves the condensation of *N*-carbamate α- and β-amino carbonyl derivatives with 1-methyl-3,5-dinitro-2-pyridone **1** under microwave irradiation. The novel chemotypes thus obtained have been gathered into three families according to morphological similarities, each group deriving from another through one unique spatial transformation. The three sets of compounds comprise a homogeneous combination of endo/exocyclic nitrogen atoms and qualify for potential bi- or tridentate binding modes. In this study, the use of microwave technology not only impacted reaction times and yields but also allowed us to access the core **12d**, the synthesis of which was not possible under conventional heating procedures. We have also reported unprecedented condensations with nonsymmetrical nitrogen-containing cyclic ketones and turned the regioselectivity issue to our advantage to simultaneously synthesize pairs of targeted chemotypes such as **12a/13a** and **12c/13c**. Further studies to broaden the scope of this reaction are now in progress and will be reported in due course.

Experimental Section

General procedure for microwave-assisted condensation reaction of **1** with various *N*-carbamate α- and β-amino carbonyls. A solution of carbonyl compound (1 mmol) and 1-methyl-3,5-dinitro-2-pyridone **1** (1.5 mmol) in methanolic ammonia (1 M, 6 mL) was irradiated at 90 °C in a sealed vial for 20−30 min. The mixture was then concentrated and dissolved in CH_2Cl_2. The organic layer was washed with saturated aqueous $NaHCO_3$ and water, dried over Na_2SO_4, and evaporated. Depending on the complexity of the separation, the residue was purified by chromatography on normal phase (using heptane/EtOAc, 9:1) or reversed phase silica (using H_2O + 0.1% AcOH/CH_3CN + 0.1% AcOH, 75:25).

***tert*-Butyl 2-(5-nitropyridin-2-yl)pyrrolidine-1-carboxylate (4a):** Obtained as a yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ (mixture of rotamers) 1.21 (s, 5H), 1.45 (s, 4H), 1.97 (m, 3H), 2.40 (m, 1H), 3.60 (m, 2H), 5.00 (m, 1H), 7.39 (m, 1H), 8.42 (m, 1H), 9.36 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (mixture of rotamers) 23.3, 24.0, 28.1 (3C), 28.3 (3C), 32.9, 34.2, 47.1, 47.4, 62.2, 62.7, 79.8, 119.9, 120.5, 131.3, 131.4, 142.8, 144.6, 144.7, 154.0, 154.6, 169.4, 170.5. Anal. Calcd for $C_{14}H_{19}N_3O_4$: C, 57.33; H, 6.53; N, 14.33; O, 21.82. Found: C, 57.33; H, 6.24; N, 14.11; O, 21.46.

***tert*-Butyl 2-(5-nitropyridin-2-yl)thiazolidine-3-carboxylate (4b):** Obtained as a pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ (mixture of rotamers) 1.33 (m, 9H), 3.07 (m, 1H), 3.24 (br s, 1H), 4.04 (m, 2H), 6.09 (m, 1H), 7.38 (d, J = 8.6 Hz, 1H), 8.44 (d, J = 7.3 Hz, 1H), 9.35 (d, J = 2.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (mixture of rotamers) 27.2 (3C), 28.8, 29.7, 49.7, 63.8, 80.2, 118.2, 130.9, 142.1, 144.0, 151.9, 152.4, 166.9, 167.3. Anal. Calcd for $C_{13}H_{17}N_3O_4S$: C, 50.15; H, 5.50; N, 13.50; O, 20.55; S, 10.30. Found: C, 50.38; H, 5.71; N, 13.09; O, 20.14; S, 10.39.

***tert*-Butyl 2-(5-nitropyridin-2-yl)cyclopentylcarbamate (5a):** Obtained as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 9H), 1.62 (m, 1H), 1.88 (m, 2H), 2.02 (m, 1H), 2.21 (m, 2H), 3.17 (m, 1H), 4.14 (quint, J = 8.0 Hz, 1H), 4.68 (d, J = 5.9 Hz, 1H), 7.43 (d, J = 8.3 Hz, 1H), 8.37 (dd, J = 8.5, 2.5 Hz, 1H), 9.35 (d, J = 1.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 28.3 (3C), 31.3, 32.9, 54.7, 58.6, 79.3, 122.3, 131.1, 142.7, 144.7, 155.2, 169.9; HRMS calcd for $C_{15}H_{22}N_3O_4$ 308.1610, found 308.1601.

Benzyl (5-nitropyridin-3-yl)methylcarbamate (7a): Obtained as a light yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.52 (d, 4.9 Hz, 2H), 5.14 (s, 2H), 5.35 (br s, 1H), 7.35 (m, 5H), 8.42 (s, 1H), 8.85 (s, 1H), 9.34 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.9, 67.3, 128.1 (2C), 128.3, 128.6 (2C), 129.9, 135.8, 136.0, 143.8, 144.3, 154.0, 156.6. Anal. Calcd for $C_{14}H_{13}N_3O_4$: C, 58.53; H, 4.56; N, 14.63; O, 22.28. Found: C, 58.30; H, 4.80; N, 14.42; O, 22.49.

***tert*-Butyl 2-(5-nitropyridin-3-yl)pyrrolidine-1-carboxylate (7b):** Obtained as a light yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ (mixture of rotamers) 1.33 (m, 9H), 1.94 (m 3H), 2.46 (br s, 1H), 3.76 (m, 2H), 4.98 (m, 1H), 8.28 (s, 1H), 8.78 (d, J = 0.9 Hz, 1H), 9.30 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (mixture of rotamers) 22.5, 22.8, 27.2 (3C), 27.4 (3C), 33.7, 34.8, 46.3, 46.4, 57.4, 57.7, 79.3, 127.0, 140.1, 140.9, 142.3, 143.3, 151.9, 153.0, 153.5; HRMS calcd for $C_{14}H_{20}N_3O_4$ 294.1454, found 294.1447.

***tert*-Butyl 3-nitro-5*H*-pyrrolo[3,4-*b*]pyridine-6(7*H*)-carboxylate (10b):** Obtained as a yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ (mixture of rotamers) 1.53 (s, 9H), 4.77 (m, 4H), 8.36 (m, 1H), 9.34 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (mixture of rotamers) 28.2 (3C), 50.0, 50.3, 52.4, 52.7, 80.7, 125.8, 126.0, 132.0, 132.3, 143.9, 145.0, 153.0, 154.1, 164.7, 164.9. Anal. Calcd for $C_{12}H_{15}N_3O_4$: C, 54.33; H, 5.70; N, 15.84; O, 24.13. Found: C, 54.33; H, 5.74; N, 15.64; O, 23.89.

***tert*-Butyl 5,6-dihydro-3-nitro-1,7-naphthyridine-7(8*H*)-carboxylate (10c):** Obtained as white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (s, 9H), 2.98 (t, J = 5.5 Hz, 2H), 3.74 (t, J = 5.7 Hz, 2H), 4.78 (s, 2H), 8.26 (br s, 1H), 9.24 (d, J = 1.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.1, 28.3 (3C), 48.7, 80.7, 131.1, 131.3, 142.6, 142.7, 154.4, 160.4. Anal. Calcd for $C_{13}H_{17}N_3O_4$: C, 55.91; H, 6.14; N, 15.04; O, 22.91. Found: C, 56.08; H, 6.34; N, 14.88; O, 22.68.

Benzyl 5,6,7,8-tetrahydro-3-nitroquinolin-7-ylcarbamate (12c): Obtained as a light yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.82 (m, 1H), 2.18 (m, 1H), 2.89 (dd, J = 18.1, 8.7 Hz, 1H), 2.97 (t, J = 6.3 Hz, 2H), 3.40 (dd, J = 18.1, 5.2 Hz, 1H), 4.13 (br s, 1H), 4.84 (br s, 1H), 5.10 (s, 2H), 7.33 (m, 5H), 8.17 (d, J = 1.6 Hz, 1H), 9.16 (d, J = 2.0 Hz, 1H). Anal. Calcd for $C_{17}H_{17}N_3O_4$: C, 62.38; H, 5.23; N, 12.84; O, 19.55. Found: C, 62.31; H, 5.58; N, 12.57; O, 19.71.

Benzyl 3,4-dihydro-7-nitro-2*H*-pyrano[3,2-*b*]pyridin-3-ylcarbamate (12d): Obtained as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.10 (dd, J = 18.1, 3.5 Hz, 1H), 3.34 (dd, J = 18.2, 5.3 Hz, 1H), 4.25 (s, 2H), 4.39 (br s, 1H), 5.02 (br s, 1H), 5.10 (s, 2H), 7.33 (m, 5H), 7.90 (d, J = 2.0 Hz, 1H), 8.98 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.9, 43.7, 67.2, 68.7, 118.6, 128.2 (2C), 128.3, 128.5 (2C), 135.8, 137.2, 143.6, 148.0, 150.3, 155.4. Anal. Calcd for $C_{16}H_{15}N_3O_5$: C, 58.36; H, 4.59; N, 12.76; O, 24.29. Found: C, 58.76; H, 4.79; N, 12.53; O, 24.12.

Benzyl 6,8-dihydro-3-nitro-5*H*-pyrano[3,4-*b*]pyridin-5-ylcarbamate (13d): Obtained as a light yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96 (dd, J = 11.9, 3.2 Hz, 1H), 4.07 (dd, J = 11.9, 2.9 Hz, 1H), 4.80 (d, J = 17.4 Hz, 1H), 4.94 (d, J = 17.4 Hz, 1H), 5.00 (m, 1H), 5.13 (d, J = 12.3 Hz, 1H), 5.17 (d, J = 12.3 Hz, 1H), 5.38 (d, J = 9.0 Hz, 1H), 7.35 (m, 5H), 8.61 (d, J = 1.6 Hz, 1H), 9.29 (d, J = 1.9 Hz, 1H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 46.7, 67.3, 68.8, 69.8, 128.1 (2C), 128.3, 128.5 (2C), 130.9, 131.8, 135.8, 143.2, 144.1, 155.8, 160.8. Anal. Calcd for $C_{16}H_{15}N_3O_5$: C, 58.36; H, 4.59; N, 12.76; O, 24.29. Found: C, 58.46; H, 4.80; N, 12.59; O, 24.08.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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