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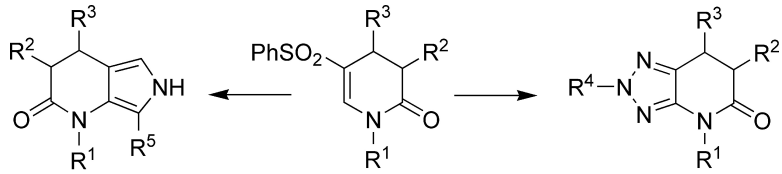

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[3 + 2] Cycloaddition Reactions in the Synthesis of Triazolo[4,5-b]pyridin-5-ones and Pyrrolo[3,4-b]pyridin-2-ones

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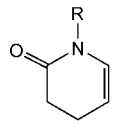
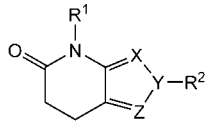
The reaction of 5-benzenesulfonyl-3,4-dihydro-1 *H*-pyridin-2-one derivatives with azides or isocyanides provided two new classes of compounds, triazolo[4,5-b]pyridin-5-ones **3** or pyrrolo[3,4-b]pyridin-2-ones **4**, respectively, in good yields and regioselectivity. A representative set of 20 compound **3** and 12 compound **4** was prepared.

Introduction

Dihydropyridinones **1** are a common occurrence in many pharmacological active substances of natural or synthetic origin.[1] They have been used in the treatment of chronic obstructive pulmonary diseases, acute coronary syndrome, acute myocardial infarction, and heart failure development[1a,b] and have also been shown to possess hepatoprotective properties.[1e] On the contrary, heterocyclic condensed dihydropyridinones are rarely studied with only a few reports on the syntheses and biological activities of pyrazolopyridinones **2** being published.[2] Our interest in the search for alternative drug structures by the isosteric replacement of atoms or groups led us to consider the triazole and pyrrole structures as possible alternatives to the pyrazole moiety in compound **2**. Hence we herein describe the syntheses of triazolo[4,5-b]pyridin-5-ones **3** and pyrrolo[3,4-b]pyridin-2-ones **4**, which to our knowledge have not been reported earlier.



1



2: X=Y=N and Z=CR^3 or X=CR^3 and Y=Z=N
3: X=Y=Z=N
4: X=CR^3, Z=CH and Y=N

Results and Discussion

Synthesis of Substituted Triazolo[4,5-*b*]pyridin-5-ones 3. 1,2,3-Triazoles are an important type of heterocyclic compound because of their numerous applications in industry, medicine, and agrochemicals.[3] They are traditionally prepared via the 1,3-dipolar cycloaddition of an alkyne and azide. However, we have recently shown that 1,2,3-trizoles can be efficiently and regioselectively prepared via [3 + 2] cycloaddition of azides and vinyl sulfones.[4] To expand this study, we have investigated the reaction using heterocyclic vinyl sulfones and azides (Scheme 1). We reasoned that such a reaction would be attractive because many vinyl sulfones are easily prepared and thermally stable and would thus possess advantage over the original nitroolefins.[5] In addition, this methodology, unlike the other methods to synthesize 1,2,3-triazoles,[6] would provide a one-pot procedure to heterocyclic fused triazoles.

To begin our studies, 3,4-dihydro-5-sulfonylpyridin-2-ones **5** were prepared from *N*-substituted-2-(phenylsulfonyl)acetamide and α,*β*-unsaturated esters according to a procedure that was reported earlier.[7] With compound **5** in hand, we proceeded to explore the [3 + 2] cycloaddition reaction by initially treating *N*-benzyl-4-methyl-5-phenylsulfonyl-3,4-dihydropyridin-2-one **5a** with sodium azide (5 equiv) in DMF at 120 °C under microwave irradiation. The reaction was incomplete after 20 min and further irradiation up to 3.5 h did not result in the complete conversion of **5a**. Hence various reaction conditions were studied (Table 1), and it was found that compound **3a** could be obtained in quantitative yield when the reaction was carried out under conventional heating at 160 °C for 2 days. To illustrate, the generality of this reaction condition, a diverse set of **3** (compounds **3a**−**3j** in Figure 1) was prepared from various compounds **5** and sodium azide. In all cases, the cycloaddition proceeded smoothly to furnish the heterocyclic fused triazoles in high yields. We next considered the N-alkylation of the triazole moiety of **3** by treating the compound with alkyl bromide in a suspension of potassium carbonate and catalytic amount of *tetra*-butyl ammonium iodide in acetone. Theoretically, the alkylation could occur on any of the three triazole nitrogens to provide a mixture of three isomeric products. However N-alkylation of **3b** with bromocyanomethane or 2-bromo-*N*-butyl-acetamide proceeded regiospecifically to give only one product, **3n** or **3p**, respectively. The NOESY spectra of **3n** and **3p** showed no interactions between the CH_2N of triazole and the CH_3 and NCH_2 groups on the 6-membered ring, thus confirming substitution at triazole N-2. Analogous N-alkylations with various compounds **3** were also performed (compounds **3k**−**3t** in Figure 1), and each gave a 2-substituted-[1,2,3]triazolo[4,5-*b*]pyridin-5(4*H*)-one as the sole product in good yield.

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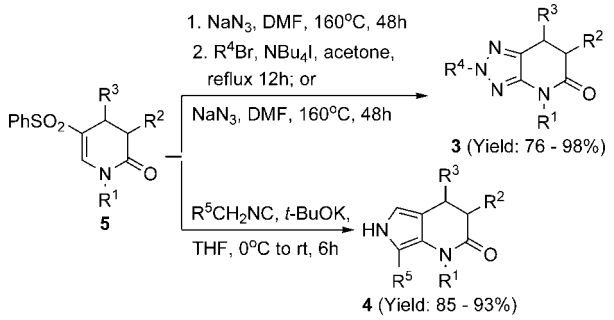
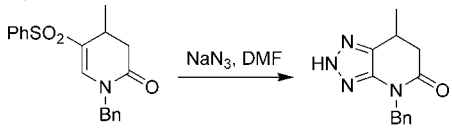
Scheme 1. Synthesis of Triazolo[4,5-*b*]pyridin-5-ones **3** and Pyrrolo[3,4-*b*]pyridin-2-ones **4**



R^1 = Bn, Bu $CH_2C_4H_3O$; R^2 = H, CH_3; R^3 = H, CH_3, Ph, $CH(CH_3)_2$
R^4 = H, Bu, Bn, CH_2CN, CH_2COPh, $CH_2CONHBu$, $CH_2CO_2CH_3$, $CH_2C_6H_{11}$; R^5 = Tos, CO_2Et,

Table 1. Synthesis of **3a**[8]



5a **3a**

temp (°C)	solvent	time	method	yield (%)[a]
120	DMF	20 min	MW	5[b]
170	DMF	20 min	MW	28[b]
180	DMF	20 min	MW	39[b]
180	DMF	3.5 h	MW	34[b]
200	DMF	1.5 h	MW	52[c]
220	DMF	20 min	MW	50[c]
135	DMF	5 days	reflux	61[b]
135	DMSO	12 h	reflux	50[b]
160	DMF	2 days	reflux	98
180	DMSO	12 h	reflux	28[c]

[a] Purified yield. [b] TLC showed an incomplete conversion of **5a**. [c] TLC showed the presence of other side products.

Synthesis of Substituted Pyrrolo[3,4-*b*]pyridin-2-ones 4. Pyrroles are commonly obtained via the Barton−Zard condensation between a nitroolefin and an alkyl isocyanoacetate.[9] However, applications of this reaction to the preparation of annulated pyrroles are less satisfactory, providing the products in low to moderate yield.[10] Thus in this study, we have investigated the pyrrole synthesis via a modified Barton−Zard condensation with heterocyclic vinyl sulfones as the pyrrole precursor. For the initial evaluation of this reaction, compound **5b** was treated with *p*-toluenesulfonylmethyl isocyanide (TosMIC) in the presence of *t*-BuOK at room temperature to give compound **4a** in 55% yield. To optimize the reaction, we carried out a systematic variation of the reaction time and temperature (Table 2). We found that the reaction proceeded more favorably at lower temperatures, and compound **4a** was obtained in 86% yield when then reaction was carried out at 0 °C and allowed to slowly warm to room temperature in 6 h. The versatility of this synthesis was demonstrated with respect to variation in the isocyanide and heterocyclic vinyl sulfone by synthesis of a small family of compounds **4** (Figure 1) in good yields. Stereochemical assignments based on NOESY and X-ray diffraction confirmed that compound **4** is the 7-substituted isomer.

In conclusion, general syntheses of annulated 1,2,3-triazoles and pyrroles have been developed. The method relies on the cycloaddition of 3,4-dihydro-5-sulfonylpyridin-2-ones **5** and affords triazolo[4,5-b]pyridin-5-ones **3** and pyrrolo[3,4-*b*]pyridin-2-ones **4** in good yields.

Experimental Section

General Procedures. All chemical reagents were obtained from commercial suppliers and were used without further purification. Analytical TLC was carried out on precoated plates (Merck silica gel 60, F254), which were visualized with UV light or stained with ninhydrin. Flash column chromatograph was performed with silica (Merck, 70–230 mesh).

^{1}H NMR and ^{13}CNMR spectra were measured at 298 K on Bruker DPX300 or Bruker AMX500 Fourier transform spectrometer and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). The number of protons (*n*) for a given resonance was indicated as *n*H. Mass spectra were performed on Finnigan MAT 95/XL-T spectrometer under electron impact (EI and ESI).

General Procedure for the Synthesis of Triazolo[4,5-*b*]pyridin-5-ones 3a−3j. To the solution of the respective compound **5** (0.5 mmol) in DMF (15 mL) was added sodium azide (25 mmol), and the reaction mixture was refluxed for 48 h. Thereafter, the reaction mixture was filtered though a small pad of Celite, concentrated to dryness, and purified by column chromatography to give the product.

4-Benzyl-6,7-dihydro-2*H*-[1,2,3]triazolo[4,5-*b*]pyridin-5(4*H*)-one 3a. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 2.80–2.83 (t, 2H, J = 7.6 Hz, CH_2CH$_2$CO), 2.93–2.96 (t, 2H, J = 7.6 Hz, CH$_2$CH_2CO), 4.94 (s, 2H, NC H_2), 7.22–7.31 (m, 5H, Ar*H*), 14.2 (br, 1H, N*H*). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 16.7, 31.4, 44.8, 127.0, 127.3, 127.7, 128.3, 137.1, 146.4, 168.2. HRMS (EI) Calcd for $C_{12}H_{12}N_4O$: 228.1011. Found: 228.1012.

4-Benzyl-7-methyl-6,7-dihydro-2*H*-[1,2,3]triazolo[4,5-*b*]pyridin-5(4*H*)-one 3b. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.24–1.26 (d, 3H, J = 6.9 Hz, CH_3), 2.54–2.59 (m, 1H, CH_2CO), 2.84–2.88 (m, 1H, CH_2CO), 3.24–3.28 (m, 1H, CH$_3$C*H*), 4.89–4.98 (m, 2H, NCH_2), 7.21–7.37 (m, 5H, Ar*H*), 14.2 (br, 1H, N*H*). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 18.6, 24.0, 39.6, 44.9, 125.5, 127.0, 127.3, 128.3, 137.1, 145.6, 168.2. HRMS (EI) Calcd for $C_{13}H_{14}N_4O$: 242.1168. Found: 242.1167.

4-Benzyl-6-methyl-6,7-dihydro-2*H*-[1,2,3]triazolo[4,5-*b*]pyridin-5(4*H*)-one 3c. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.20–1.23 (d, 3H, J = 7.0 Hz, CH_3), 2.64–2.72 (m, 1H, CH_2CH), 2.84–2.92 (m, 1H, C*H*CO), 3.09–3.36 (m, 1H, CH_2CH), 4.90–5.00 (m, 2H, NCH_2), 7.22–7.32 (m, 5H, Ar*H*), 14.2 (br, 1H, N*H*). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.5, 24.6, 36.1, 45.2, 127.0, 127.3, 127.8, 128.3, 137.2, 146.1, 171.1. HRMS (EI) Calcd for $C_{13}H_{14}N_4O$: 242.1168. Found: 242.1168.

4-Benzyl-7-phenyl-6,7-dihydro-2*H*-[1,2,3]triazolo[4,5-*b*]pyridin-5(4*H*)-one 3d. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 2.93–2.98 (m, 1H, CH_2CO), 3.17–3.22 (m, 1H, CH_2CO), 4.51–4.54 (t, 1H, J = 6.8 Hz, C*H*Ph), 4.93–5.05 (m, 2H, NCH_2), 7.15–7.31 (m, 10H, Ar*H*). ^{13}C NMR (DMSO-d_6,125

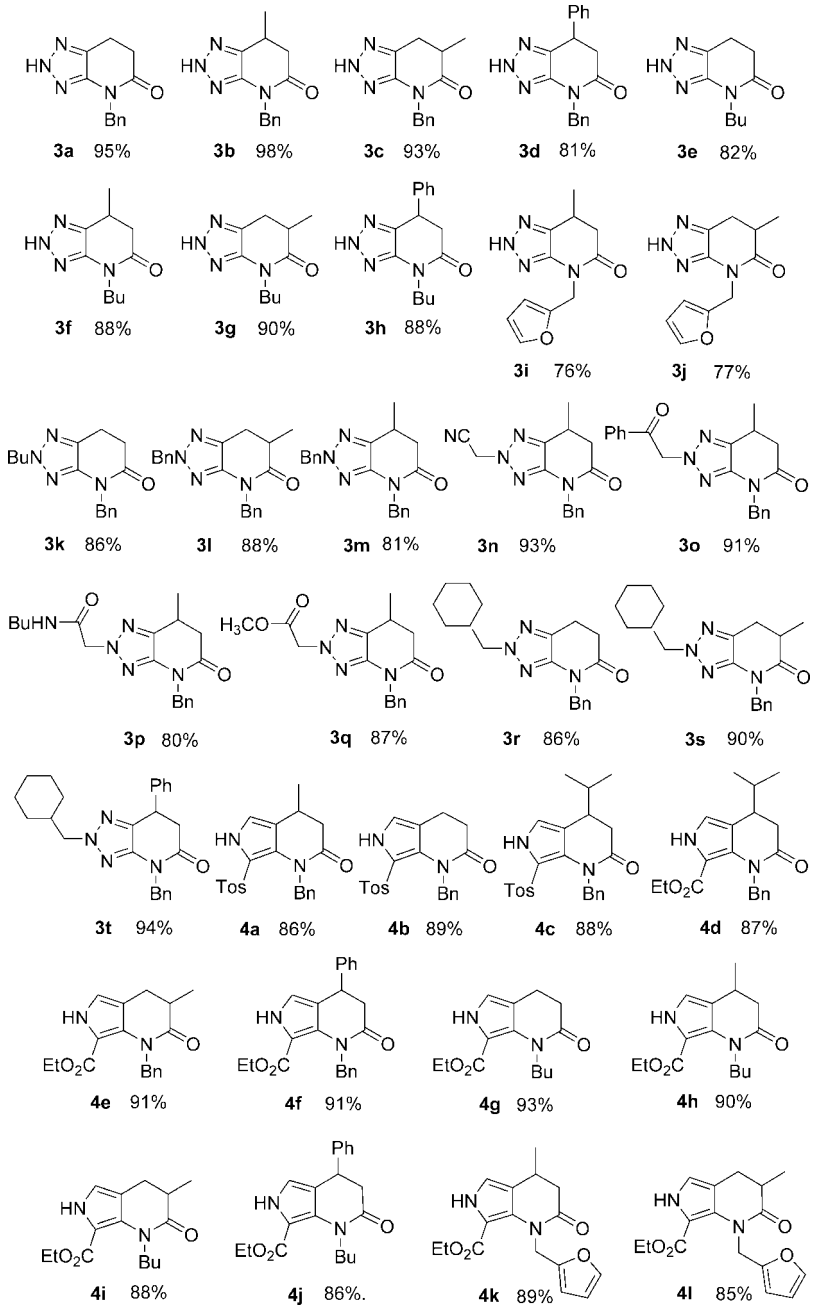
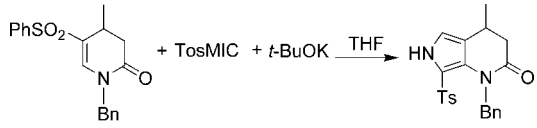


Figure 1. Library of **3** and **4**.

Table 2. Cycloaddition of Cyclic Vinylsulfones **1** and TosMIC



5b B C **4a**

entry	**5b**/B/C	temp	time	yield[a]
1	1:3:3	RT	5 h	55%
2	1:3:3	MW, 62 °C	5 min	21%
3	1:3:3	0 °C to RT	6 h	81%

[a] Purified yield.

MHz): δ 34.4, 40.1, 45.0, 127.0, 127.1(×2), 127.2, 127.4, 128.3, 128.6, 132.9, 141.2, 146.2, 167.7. HRMS (EI) Calcd for $C_{18}H_{16}N_4O$: 304.1324. Found: 304.1328.

4-Butyl-6,7-dihydro-3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-5(4*H*)-one 3e. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 0.86–0.89 (t, 3H, J = 6.9 Hz, $CH_2CH_2CH_2CH_3$), 1.24–1.30 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.52–1.58 (m, 2H, $CH_2CH_2CH_2CH_3$), 2.69–2.72 (t, 2H, J = 7.6 Hz, CH_2CH_2CO), 2.87–2.90 (t, 2H, J = 7.6 Hz, CH_2CH_2CO), 3.72–3.75 (t, 2H, J = 7.6 Hz, $CH_2CH_2CH_2CH_3$), 14.1(br, 1H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 13.6, 16.8, 19.4, 29.1, 31.4, 41.25, 129.9, 146.5, 167.9. HRMS (EI) Calcd for $C_9H_{14}N_4O$:194.1168. Found: 194.1172.

4-Butyl-7-methyl-6,7-dihydro-3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-5(4*H*)-one 3f. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 0.86–0.88 (t, 3H, J = 7.6 Hz, $CH_2CH_2CH_2CH_3$), 1.21–1.28 (m, 5H, $CH_2CH_2CH_2CH_3$ + CH_3), 1.52–1.58 (m, 2H, $CH_2CH_2CH_2CH_3$), 2.41–2.50 (m, 1H, CH_2CO), 2.74–2.78 (m, 1H, CH_2CO), 3.15–3.22 (m, 1H, $CHCH_3$), 3.67–3.79 (m, 2H, $CH_2CH_2CH_2CH_3$), 14.1 (br, 1H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 13.6, 18.6, 19.4, 24.0, 29.1, 40.0, 41.2,

134.7, 145.6, 167.8. HRMS (EI) Calcd for $C_{10}H_{16}N_4O$: 208.1324. Found: 208.1324.

4-Butyl-6-methyl-6,7-dihydro-3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-5(4*H*)-one 3g. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 0.85–0.90 (t, 3H, J = 7.4 Hz, $CH_2CH_2CH_2CH_3$), 1.15–1.29 (m, 5H, $CH_2CH_2CH_2CH_3$ + CH_3), 1.50–1.58 (m, 2H, $CH_2CH_2CH_2CH_3$), 2.56–2.80 (m, 2H, CH_2 + $CHCH_3$), 3.00–3.08 (m, 1H, CH_2), 3.67–3.81 (m, 2H, $CH_2CH_2CH_2CH_3$), 14.15 (br, 1H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 13.6, 16.6, 19.4, 24.6, 29.1, 36.0, 41.6, 129.2, 145.2, 170.8. HRMS (EI) Calcd for $C_{10}H_{16}N_4O$: 208.1324. Found: 208.1326.

4-Butyl-7-phenyl-6,7-dihydro-2*H*-[1,2,3]triazolo[4,5-*b*]pyridin-5(4*H*)-one 3h. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 0.87–0.90 (t, 3H, J = 7.0 Hz, $CH_2CH_2CH_2CH_3$), 1.23–1.31 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.56–1.62 (m, 2H, $CH_2CH_2CH_2CH_3$), 2.83–2.88 (m, 1H, CH_2CO), 3.07–3.12 (m, 1H, CH_2CO), 3.75–3.84 (m, 2H, $CH_2CH_2CH_2CH_3$), 4.46–4.49 (t, 1H, J = 7.0 Hz, CHAr), 7.17–7.33(m, 5H, ArH), 14.3(br, 1H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 13.6, 19.4, 29.1, 34.4, 40.0, 41.3, 125.7, 126.9, 127.0, 128.6, 141.4, 146.4, 167.4. HRMS (ESI, M − H) Calcd for $C_{15}H_{17}N_4O$: 269.1402. Found: 269.1400.

4-(Furan-2-ylmethyl)-7-methyl-6,7-dihydro-2*H*-[1,2,3]triazolo[4,5-*b*]pyridin-5(4*H*)-one 3i. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.23–1.24 (d, 3H, J = 6.3 Hz, CH_3), 2.49–2.54 (m, 1H, CH_2CO), 2.81–2.85 (m, 1H, CH_2CO), 3.19–3.26 (m, 1H, $CHCH_3$), 4.89–4.97 (m, 2H, NCH_2), 6.26–7.53 (m, 3H, $H_{furanyl}$), 14.25 (br, 1H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 18.6, 24.0, 38.3, 40.0, 107.9, 110.5, 134.6, 142.2, 145.3, 150.2, 167.9. HRMS (ESI, M − H) Calcd for $C_{11}H_{11}N_4O_2$: 232.0882. Found: 232.0880.

4-(Furan-2-ylmethyl)-6-methyl-6,7-dihydro-2*H*-[1,2,3]triazolo[4,5-*b*]pyridin-5(4 *H*)-one 3j. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.18–1.20 (d, 3H, J = 7.0 Hz, CH_3), 2.61–2.67 (m, 1H, CH_2CH), 2.79–2.87 (m, 1H, CH), 3.04–3.09 (m, 1H, CH_2CH), 4.88–4.96 (m, 2H, NCH_2), 6.24–7.52 (m, 3H, $H_{furanyl}$) 14.2 (br, 1H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 16.4, 24.6, 36.1, 40.0, 107.8, 110.5, 129.5, 142.2, 145.8, 150.2, 170.8. HRMS (ESI, M − H) Calcd for $C_{11}H_{11}N_4O_2$: 232.0882. Found: 232.0875.

General Procedure of the Synthesis of N-Substituted 1,2,3-Triazoles 3k−3t. To a solution of the respective triazole (0.2 mmol) in acetone (5 mL) was added potassium carbonate (1 mmol), alkyl bromide (1 mmol), and a catalytic amount of N(*n*-Bu)$_4$I. The reaction mixture was heated to reflux under nitrogen overnight. Thereafter the reaction mixture was concentrated and purified by column chromatography.

4-Benzyl-2-butyl-6,7-dihydro-2*H*-[1,2,3]triazolo[4,5-*b*]pyridin-5(4*H*)-one 3k. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.85–0.88 (t, 2H, J = 7.6 Hz, $CH_2CH_2CH_2CH_3$), 1.22–1.28 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.76–1.82 (m, 2H, $CH_2CH_2CH_2CH_3$), 2.75–2.78 (m, 2H, CH_2CH_2CO), 2.87–2.90 (m, 2H, CH_2CH_2CO), 4.17–4.20 (t, 2H, $CH_2CH_2CH_2CH_3$), 4.94 (s, 2H, NCH_2Ar), 7.17–7.36 (m, 5H, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.5, 17.6, 19.7, 31.7, 32.1, 45.8, 54.5, 127.4, 128.3, 128.6, 130.1, 136.9, 146.7, 168.4. HRMS (EI) Calcd for $C_{16}H_{20}N_4O$: 284.1637. Found: 284.1643.

2,4-Dibenzyl-6-methyl-6,7-dihydro-2*H*-[1,2,3]triazolo[4,5-*b*]pyridin-5(4*H*)-one 3l. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.24–1.25 (d, 3H, J = 6.9 Hz, CH_3), 2.54–2.59 (m, 1H, CH_2CH), 2.72–2.78 (m, 1H, CH), 2.97–3.02 (m, 1H, CH_2CH), 4.90–4.96 (m, 2H, NCH_2), 5.34 (s, 2H, NCH_2), 7.16–7.33 (m, 10H, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 16.8, 25.7, 36.9, 46.1, 58.4, 127.4, 127.9, 128.2, 128.3, 128.6, 128.7, 131.0, 135.6, 137.0, 147.0, 171.4. HRMS (EI) Calcd for $C_{20}H_{20}N_4O$: 332.1637. Found: 332.1642.

2,4-Dibenzyl-7-methyl-6,7-dihydro-2*H*-[1,2,3]triazolo[4,5-*b*]pyridin-5(4*H*)-one 3m. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.22–1.24 (d, 3H, J = 7.0 Hz, CH_3), 2.40–2.46 (m, 1H, CH_2CO), 2.76–2.81 (m, 1H, CH_2CO), 3.08–3.15 (m, 1H, CH), 4.89–4.96 (m, 2H, NCH_2), 5.30–5.36 (m, 2H, NCH_2), 7.13–7.30 (m, 10H, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 18.8, 24.9, 40.6, 45.7, 58.4, 127.4, 127.8, 128.1, 128.3, 128.5, 128.6, 135.6, 136.0, 136.8, 146.3, 168.4. HRMS (EI) Calcd for $C_{20}H_{20}N_4O$: 332.1637. Found: 332.1640.

2-(4-Benzyl-7-methyl-5-oxo-4,5,6,7-tetrahydro-[1,2,3]triazolo[4,5-*b*]pyridin-2-yl)acetonitrile 3n. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.28–1.30 (d, 3H, J = 7.0 Hz, CH_3), 2.46–2.52 (m, 1H, CH_2CO), 2.83–2.88 (m, 1H, CH_2CO), 3.16–3.20 (m, 1H, CH), 4.91–4.98 (m, 2H, NCH_2Ph), 5.09 (s, 2H, CH_2), 7.17–7.20 (m, 5H, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 18.4, 24.9, 40.2, 41.8, 45.9, 112.9, 127.6, 128.3, 128.4, 136.3, 138.7, 148.0, 168.1. HRMS (EI) Calcd for $C_{15}H_{15}N_5O$: 281.1277. Found: 281.1279.

4-Benzyl-7-methyl-2-(2-oxo-2-phenylethyl)-2,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-*b*]pyridin-5-one 3o. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.26–1.27 (d, 3H, J = 6.7 Hz, CH_3), 2.44–2.50 (m, 1H, CH_2CO), 2.80–2.85 (m, 1H, CH_2CO), 3.14–3.22 (m, 1H, CH), 4.88–4.97 (m, 2H, CH_2Ar), 5.59–5.66 (m, 2H, CH_2), 7.12–7.84 (m, 10H, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 18.5, 24.9, 40.5, 45.8, 60.0, 127.4, 128.0, 128.2, 128.3, 128.9, 134.1, 134.2, 136.7, 136.9, 147.0, 168.4, 191.6. HRMS (EI) Calcd for $C_{21}H_{20}N_4O_2$: 360.1586. Found: 360.1588.

2-(4-Benzyl-7-methyl-5-oxo-4,5,6,7-tetrahydro-[1,2,3]triazolo[4,5-*b*]pyridin-2-yl)-*N*-butylacetamide 3p. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.79–0.82 (t, 3H, J = 7.0 Hz, $CH_2CH_2CH_2CH_3$), 1.14–1.19 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.20–1.30 (m, 5H, $CH_2CH_2CH_2CH_3$+ CH_3), 2.48–2.53 (m, 1H, CH_2CO), 2.85–2.89 (m, 1H, CH_2CO), 3.08–3.24 (m, 3H, $CH_2CH_2CH_2CH_3$+CH), 4.86 (s, 2H, NCH_2), 4.95 (m, 2H, NCH_2), 5.71 (br, 1H, NH), 7.17–7.32 (m, 5H, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.6, 18.6, 19.9, 24.9, 31.3, 39.3, 40.4, 45.7, 57.3, 127.6, 128.3, 128.5, 136.5, 137.2, 147.3, 165.8, 168.3. HRMS (EI) Calcd for $C_{19}H_{25}N_5O_2$: 355.2008. Found: 355.2003.

Methyl 2-(4-benzyl-7-methyl-5-oxo-4,5,6,7-tetrahydro-[1,2,3]triazolo[4,5-*b*]pyridin-2-yl)acetate 3q. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.27–1.28 (d, 3H, J = 6.9 Hz, CH_3CH), 2.46–2.51 (m, 1H, CH_2CO), 2.82–2.86 (m, 1H, CH_2CO), 3.15–3.22 (m, 1H, CH), 3.70 (s, 3H, OCH_3), 4.93–4.95 (m, 2H, NCH_2Ph), 4.98 (s, 2H, NCH_2), 7.15–7.33 (m, 5H, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 18.5, 24.9, 40.5, 40.9, 52.7, 55.1, 127.5, 128.4 (×2), 136.7, 137.1, 147.1, 167.6, 168.4. HRMS (M + Na) Calcd for $C_{16}H_{18}N_4NaO_3$: 337.1277. Found: 337.1275.

4-Benzyl-2-(cyclohexylmethyl)-6,7-dihydro-2*H*-[1,2,3]triazolo[4,5-*b*]pyridin-5(4*H*)-one 3r. ^{1}H NMR ($CDCl_3$, 500

MHz): δ 0.86–1.67 (m, 10H, 5CH_2), 1.80–1.86(m, 1H, C*H*), 2.74–2.90(m, 4H, CH_2CH_2), 4.00–4.02 (d, 2H, J = 7.6 Hz, CHCH_2), 4.94 (s, 2H, NCH_2Ph), 7.14–7.36(m, 5H, Ar*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 17.6, 25.6, 26.2, 30.4, 32.1, 38.6, 45.7, 60.8, 127.4, 128.3, 128.7, 130.0, 136.9, 146.6, 168.4. HRMS (EI) Calcd for $C_{19}H_{24}N_4O$: 324.1950. Found: 324.1944.

4-Benzyl-2-(cyclohexylmethyl)-6-methyl-6,7-dihydro-2*H*-[1,2,3]triazolo[4,5-*b*]pyridin-5(4*H*)-one 3s. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.85–1.66 (m, 13H, 5CH_2 + CH_3), 1.81–1.89 (m, 1H, C*H*), 2.54–2.59 (m, 1H, CH_2CHCO), 2.72–2.79 (m, 1H, CH$_2$C*H*CO), 2.97–3.02 (m, 1H, CH_2CHCO), 4.00–4.02 (d, 2H, CHCH_2), 4.90–4.97 (m, 2H, NC H_2Ph), 7.15–7.35 (m, 5H, Ar*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 16.8, 25.6, 26.2, 29.7, 30.4, 37.0, 38.6, 46.0, 60.8, 127.4, 128.3, 128.6, 129.9, 137.0, 146.3, 171.4. HRMS (EI) Calcd for $C_{20}H_{26}N_4O$: 338.2107. Found: 338.2105.

4-Benzyl-2-(cyclohexylmethyl)-7-phenyl-6,7-dihydro-2*H*-[1,2,3]triazolo[4,5-*b*]pyridin-5(4*H*)-one 3t. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.86–1.64 (m, 10H, 5CH_2), 1.80–1.84 (m, 1H, C*H*), 2.88–2.93 (m, 1H, CH_2CO), 3.04–3.08 (m, 1H, CH_2CO), 3.98–4.05 (m, 2H, NCH_2), 4.28–4.31 (t, 2H, J = 7.0 Hz, C*H*Ph), 4.92–5.05 (m, 2H, NCH_2), 7.03–7.35 (m, 10H, Ar*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 25.6, 26.2, 30.4, 35.8, 38.6, 40.9, 45.8, 61.0, 127.1, 127.3, 127.5, 128.3, 128.8, 128.9, 133.0, 136.7, 140.6, 146.5, 167.8. HRMS (EI) Calcd for $C_{25}H_{28}N_4O$: 400.2263. Found: 400.2263.

General Procedure for the Synthesis of Pyrrolo[3,4-*b*]pyridin-2-ones 4a−4l. The respective isocyanide (1.5 mmol) was added to a 1.0 M solution of potassium *tert*-butoxide in THF (1.5 mmol) via a syringe at 0 °C under nitrogen. To this reaction mixture at 0 °C was added dropwise a solution of the respective vinylsulfone (0.5 mmol) in dry THF (0.1 M vinylsulfone in THF), and the reaction mixture was stirred and allowed to warm slowly to room temperature. The reaction was monitored by TLC and was observed to be complete after 6 h. Thereafter, the reaction was quenched with saturated aqueous ammonium chloride aqueous solution and extracted with ethyl acetate. The combined organic layer was washed with brine (30 mL × 2), dried with $MgSO_4$, concentrated to dryness, and purified by column chromatography.

1-Benzyl-4-methyl-7-tosyl-3,4-dihydro-1*H*-pyrrolo[3,4-*b*]pyridin-2(6*H*)-one 4a. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.13–1.14 (d, 3H, J = 6.9 Hz, CH_3CH), 2.28 (s, 3H, PhCH_3), 2.30–2.32 (m, 1H, CH_2CO), 2.50–2.58 (m, 1H, CH_2CO), 2.89–2.94 (m, 1H, CH$_3$C*H*), 5.08–5.27 (m, 2H, NCH_2), 6.77–7.48 (m, 10H, Ar*H*), 11.78 (br, 1H, N*H*). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 18.7, 20.9, 24.5, 40.0, 40.7, 112.8, 118.7, 119.0, 125.7, 125.8, 126.2, 127.8, 128.0, 129.6, 137.6, 139.4, 143.3, 170.1. HRMS (ESI, M-H) Calcd for $C_{22}H_{21}N_2O_3S$: 393.1273. Found: 393.1272.

1-Benzyl-7-tosyl-3,4-dihydro-1*H*-pyrrolo[3,4-*b*]pyridin-2(6*H*)-one 4b. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 2.27 (s, 3H, PhCH_3), 2.54–2.57 (t, 2H, J = 7.6 Hz, CH_2CH$_2$CO), 2.67–2.69 (t, 2H, J = 7.6 Hz, CH$_2$CH_2CO), 5.19 (s, 2H, NCH_2), 6.77–7.46 (m, 10H, Ar*H*), 11.74 (br, 1H, N*H*). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 17.5, 20.9, 32.8, 46.9, 112.7, 113.2, 119.5, 125.5, 125.6, 126.1, 127.9, 129.6, 130.6, 137.5, 139.4, 143.2, 170.2. HRMS (EI) Calcd for $C_{21}H_{20}N_2O_3S$: 380.1195. Found: 380.1186.

1-Benzyl-4-isopropyl-7-tosyl-3,4-dihydro-1*H*-pyrrolo[3,4-*b*]pyridin-2(6*H*)-one 4c. ^{1}H NMR (DMF-d_7, 500 MHz): δ 0.79–0.85 (m, 6H, CH_3CHCH_3), 1.58–1.65 (m, 1H, CH$_3$-C*H*CH$_3$), 2.33 (s, 3H, PhCH_3), 2.49–2.64 (m, 3H, CO-CH_2C*H*), 5.25–5.30 (m, 2H, NCH_2), 6.93–7.61 (m, 10H, Ar*H*), 11.83 (br, 1H, N *H*). ^{13}C NMR (DMF-d_7, 125 MHz): δ 19.1, 20.5, 21.2, 30.4, 36.4, 37.4, 48.4, 114.2, 117.3, 120.8, 126.8, 127.1, 127.5, 128.5, 130.5, 131.4, 138.8, 140.8, 144.3, 171.0. HRMS (EI) Calcd for $C_{24}H_{26}N_2O_3S$: 422.1664. Found: 422.1663.

Ethyl 1-Benzyl-4-isopropyl-2-oxo-2,3,4,6-tetrahydro-1*H*-pyrrolo[3,4-*b*]pyridine-7-carboxylate 4d. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.73–0.81 (m, 6H, CH_3CHCH_3), 1.18–1.19 (t, 3H, J = 7.0 Hz, OCH$_2$CH_3), 1.59–1.63 (m, 1H, CH$_3$C*H*CH$_3$), 2.46–2.61 (m, 3H, COCH_2C*H*), 4.14–4.18 (m, 2H, OCH_2CH$_3$), 5.46 (s, 2H, NCH_2), 6.44–6.45 (d, 1H, J = 3.2 Hz, $H_{pyrrole}$), 7.04–7.18 (m, 5H, Ar*H*), 8.91 (br, 1H, N*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 14.3, 18.8, 20.3, 29.7, 36.0, 36.7, 47.0, 60.4, 109.2, 117.1, 117.6, 126.6, 127.6, 127.9, 132.2, 138.2, 159.4, 171.3. HRMS (EI) Calcd for $C_{20}H_{24}N_2O3$: 340.1787. Found: 340.1788.

Ethyl 1-Benzyl-3-methyl-2-oxo-2,3,4,6-tetrahydro-1*H*-pyrrolo[3,4-*b*]pyridine-7-carboxylate 4e. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.19–1.20 (m, 6H, CH$_2$CHCH_3 + OCH$_2$CH_3), 2.34–2.38 (m, 1H, CH_2CHCH$_3$), 2.62–2.74 (m, 2H, CH_2C*H*CH$_3$), 4.15–4.19 (m, 2H, OCH_2CH$_3$), 5.43–5.55 (m, 2H, NCH_2), 6.50–6.51 (d, 1H, J = 3.2 Hz, $H_{pyrrole}$), 7.05–7.19 (m, 5H, Ar*H*), 8.58 (br, 1H, N*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 14.4, 15.8, 26.0, 37.3, 47.4, 60.5, 109.2, 113.5, 117.1, 126.5, 127.0, 128.1, 132.4, 138.6, 159.4, 173.9. HRMS (EI) Calcd for $C_{18}H_{20}N_2O3$: 312.1474. Found: 312.1465.

Ethyl 1-Benzyl-2-oxo-4-phenyl-2,3,4,6-tetrahydro-1*H*-pyrrolo[3,4-*b*]pyridine-7-carboxylate 4f. ^{1}HNMR ($CDCl_3$, 300 MHz): δ 1.17–1.22 (t, 3H, J = 7.3 Hz, OCH$_2$CH_3), 2.84–2.87 (m, 2H, CH_2CO), 3.98–4.04 (m, 1H, C*H*Ph), 4.14–4.21 (m, 2H, OCH_2CH$_3$), 5.46–5.58 (m, 2H, NCH_2), 6.20–6.21 (d, 1H, J = 6.9 Hz, $H_{pyrrole}$), 7.03–7.17 (m, 10H, Ar*H*), 8.84 (br, 1H, N*H*). ^{13}CNMR ($CDCl_3$, 75 MHz): δ 14.3, 36.1, 41.1, 46.7, 60.5, 109.4, 117.8, 118.0, 126.7, 127.0, 127.4, 127.6, 128.0, 128.6, 131.9, 138.1, 141.1, 159.4, 170.4. HRMS (EI) Calcd for $C_{18}H_{20}N_2O3$: 374.1630. Found: 374.1643.

Ethyl 1-Butyl-2-oxo-2,3,4,6-tetrahydro-1*H*-pyrrolo[3,4-*b*]pyridine-7-carboxylate 4g. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.77–0.82 (t, 3H, J = 7.4 Hz, CH$_2$CH$_2$CH$_2$CH_3), 1.15–1.48 (m, 7H, OCH$_2$CH_3+CH$_2$CH$_2$CH_2CH$_3$), 2.52–2.61 (m, 4H, J = 7.0 Hz, COCH_2CH_2), 4.18–4.27 (m, 4H, CH_2CH$_2$CH$_2$CH$_3$+ OCH_2CH$_3$), 6.56–6.57 (d, 1H, J = 3.2 Hz, $H_{pyrrole}$), 8.80 (br, 1H, N*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.8, 14.4, 18.1, 19.8, 29.7, 33.7, 43.9, 60.4, 109.1, 114.2, 116.9, 132.4, 159.3, 171.2. HRMS (EI) Calcd for $C_{14}H_{20}N_2O_3$: 264.1474. Found: 264.1470.

Ethyl 1-Butyl-4-methyl-2-oxo-2,3,4,6-tetrahydro-1*H*-pyrrolo[3,4-*b*]pyridine-7-carboxylate 4h. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.85–0.88 (t, 3H, J = 7.6 Hz, CH$_2$CH$_2$CH$_2$CH_3), 1.22–1.29 (m, 5H, CH$_2$CH$_2$CH_2CH$_3$ + CH$_2$CHCH_3), 1.33–1.36 (t, 3H, J = 7.0 Hz, OCH$_2$CH_3), 1.47–1.53 (m, 2H, CH$_2$CH_2CH$_2$CH$_3$), 2.28–2.33 (m, 1H, CH_2CO), 2.62–2.66 (m,

1H, CH_2CO), 2.88–2.95 (m, 1H, CH_2CHCH_3), 4.21–4.34 (m, 4H, $CH_2CH_2CH_2CH_3 + OCH_2CH_3$), 6.61–6.62 (d, 1H, $J = 3.2$ Hz, $H_{pyrrole}$), 8.72 (br, 1H, N*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.9, 14.5, 19.0, 19.9, 25.0, 29.7, 41.8, 43.8, 60.5, 109.2, 116.0, 120.4, 131.8, 159.3, 170.9. HRMS (EI) Calcd for $C_{15}H_{22}N_2O_3$: 278.1630. Found: 278.1629.

Ethyl 1-Butyl-3-methyl-2-oxo-2,3,4,6-tetrahydro-1 *H*-pyrrolo[3,4-*b*]pyridine-7-carboxylate 4i. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.84–0.87 (t, 3H, $J = 7.6$ Hz, $CH_2CH_2CH_2CH_3$), 1.20–1.28 (m, 5H, $CH_2CH_2CH_2CH_3$ + COCHCH_3), 1.33–1.36 (t, 3H, $J = 7.0$ Hz, OCH_2CH_3), 1.46–1.52 (m, 2H, $CH_2CH_2CH_2CH_3$), 2.35–2.40 (m, 1H, CH_2CHCO), 2.57–2.64 (m, 1H, COC*H*CH_3), 2.71–2.75 (m, 1H, CH_2CHCO), 4.20–4.32 (m, 4H, $CH_2CH_2CH_2CH_3 + OCH_2CH_3$), 6.61–6.62 (d, 1H, $J = 3.2$ Hz, $H_{pyrrole}$), 8.75 (br, 1H, N*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.9, 14.4, 15.7, 19.8, 26.0, 29.8, 37.3, 44.3, 60.4, 108.9, 113.5, 117.1, 132.3, 159.3, 173.7. HRMS (EI) Calcd for $C_{15}H_{22}N_2O_3$: 278.1630. Found: 278.1633.

Ethyl 1-Butyl-2-oxo-4-phenyl-2,3,4,6-tetrahydro-1*H*-pyrrolo[3,4-*b*]pyridine-7-carboxylate 4j. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.78–0.81 (t, 3H, $J = 7.6$ Hz, $CH_2CH_2CH_2CH_3$), 1.16–1.22 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.27–1.30 (t, 3H, $J = 7.0$ Hz, OCH_2CH_3), 1.39–1.46 (m, 2H, $CH_2CH_2CH_2CH_3$), 2.76–2.80 (m, 2H, CH_2CO), 3.99–4.02 (m, 1H, C*H*Ph), 4.18–4.30 (m, 4H, $CH_2CH_2CH_2CH_3 + OCH_2CH_3$), 6.28–6.29 (d, 1H, $J = 3.2$ Hz, $H_{pyrrole}$), 7.14–7.26 (m, 5H, Ar*H*), 8.75 (br, 1H, N*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.9, 14.4, 19.9, 29.8, 36.3, 41.3, 44.0, 60.6, 109.2, 117.7, 118.4, 127.1, 127.4, 128.7, 132.1, 141.4, 159.3, 170.3. HRMS (EI) Calcd for $C_{20}H_{24}N_2O_3$: 340.1787. Found: 340.1789.

Ethyl 1-(Furan-2-ylmethyl)-4-methyl-2-oxo-2,3,4,6-tetrahydro-1*H*-pyrrolo[3,4-*b*]pyridine-7-carboxylate 4k. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.10–1.11(d, 3H, $J = 6.3$ Hz, CHCH_3), 1.26–1.29 (t, 3H, $J = 7.0$ Hz, OCH_2CH_3), 2.31–2.34 (m, 1H, CH_2CO), 2.60–2.64 (m, 1H, CH_2CO), 2.81–2.88 (m, 1H, C*H*), 4.23–4.27 (m, 2H, OCH_2CH_3), 5.50–5.57(m, 2H, NCH_2), 6.00–7.14 (m, 4H, $H_{furanyl} + H_{pyrrole}$), 8.85 (br, 1H, N*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 14.4, 19.0, 24.8, 39.8, 41.5, 60.5, 107.7, 109.4, 109.9, 116.0, 120.2, 131.0, 141.6, 151.5, 159.5, 171.0. HRMS (ESI, M + Na) Calcd for $C_{16}H_{18}N_2NaO_4$: 325.1164. Found: 325.1163.

Ethyl 1-(Furan-2-ylmethyl)-3-methyl-2-oxo-2,3,4,6-tetrahydro-1*H*-pyrrolo[3,4-*b*]pyridine-7-carboxylate 4l. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.18–1.20(d, 3H, $J = 7.0$ Hz, CHCH_3), 1.27–1.30 (t, 3H, $J = 6.9$ Hz, OCH_2CH_3), 2.30–2.35 (m, 1H, $CHCH_2$), 2.55–2.70 (m, 2H, CH_2CH + C*H*CH_2), 4.23–4.27 (m, 2H, OCH_2CH_3), 5.47–5.58(m, 2H, NCH_2), 5.98–7.20 (m, 4H, $H_{furanyl} + H_{pyrrole}$), 8.56 (br, 1H, N*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 14.4, 15.7, 25.9, 37.3, 40.4, 60.6, 107.5, 109.1, 109.9, 113.5, 117.0, 131.8, 141.6, 151.8, 159.5, 173.7. HRMS (ESI, M + Na) Calcd for $C_{16}H_{18}N_2NaO_4$: 325.1164. Found: 325.1157.

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Supporting Information Available. ^{1}H and ^{13}C NMR spectra of compounds **3** and **4**, NOESY spectra of **3n**, **3p**, **4e**, and **4i**, and X-ray crystal structures of **4c** and **4d**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

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