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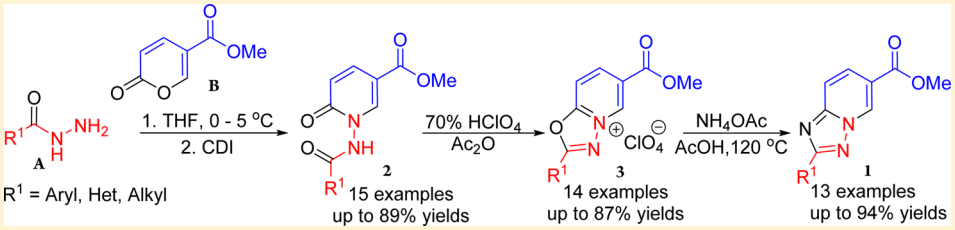
Cyclization of Methyl-Coumalate-Derived Methyl 1-Benzamido-6-oxo-1,6-dihydropyridine-3-carboxylates: Assembly of the [1,2,4]Triazolo[1,5-*a*]pyridine Ring System

Harold Moloney,*,* Nicholas A. Magnus, Jonas Y. Buser, and Matthew C. Embry

Small Molecule Design and Development, Eli Lilly and Company, Indianapolis, Indiana 46285, United States

Supporting Information



ABSTRACT: An efficient three-step synthesis of a series of fused bicyclic *s*-[1,2,4]triazolo[1,5-*a*]pyridines **1** was accomplished utilizing novel intermediates derived from inexpensive, commercially available hydrazides **A** and methyl coumalate **B**. A significant feature of this approach was the formation of a dihydrazide intermediate **2**, bypassing the need for oxidative N−N bond formation in the 1,2,4-triazole synthesis. Further purification of the dihydrazides **2**, beyond simple isolation, proved to be unnecessary owing to the impurity rejection afforded by the crystalline oxadiazolium salts **3**. Additionally, the prepared oxadiazolium perchlorate salts showed excellent moisture stability, an unusual feature in compounds of this type.

INTRODUCTION

The *s*-[1,2,4]triazolo[1,5-*a*]pyridine system represents a structural core associated with a diverse range of biologically important small molecules. Reports in the scientific literature have made reference to its properties in the inhibition of JAK1,[1] JAK2,[2] and Pi3K,[3−5] as antibacterial and antimicrobial agents[6−9] and its association with anticancer properties.[10] This pharmacologically active subunit is also frequently mentioned in patent literature; selected examples mention its properties of JAK2 inhibition,[2] mGlu 2 modulation,[11] treatment of cardiovascular disorders,[12] type 2 diabetes,[13,14] in the treatment of hyperproliferative disorders,[15] PDE10 inhibitors,[16] and for its herbicidal effects.[17] Despite the plethora of therapeutic areas associated with this heterocyclic system, relatively few distinct synthetic strategies exist for its construction (see reference 18 and references contained therein). The 1,2,4−triazole moiety does not contain two adjacent carbon atoms, thus to form a fused-ring system, one of the nitrogen ring atoms must also be a component of the second ring. Bearing this in mind, it is unsurprising that the most frequently encountered substrates in its production are the 2-amino pyridines. 2-Amino pyridines are industrially important feedstock chemicals; however, they present sustainability issues because of their derivation from petroleum sources.[19] The use of these starting materials results in scope limitations due to the requirement for an oxidative N−N bond formation, frequently utilizing stoichiometric quantities of oxidant. Oxidants such as lead tetraacetate,[20] $Cu(OAc)_2$,[21] MnO_2 (4 equiv),[6] NaClO,[22] and PPA[23] have all been used to varying degrees of success to close the triazole ring via N−N bond formation. More recent examples include heterogeneous transition-metal-catalyzed cyclization strategies utilizing copper(I) bromide with molecular oxygen as the oxidant[21] and a catalyzed oxidation.[24] A variety of hypervalent iodine-mediated metal-free alternatives have also been disclosed,[25,26] although being more environmentally friendly than the aforementioned metal-mediated routes, suffer from the same lack of scope on the pyridine ring.

Previously disclosed work from our medicinal chemistry laboratories[13] has described the synthesis of a series of molecules containing the *s*-[1,2,4]triazolo[1,5-*a*]pyridine moiety, which was under investigation for their GPR40 activation properties. The *s*-[1,2,4]triazolo[1,5−1]pyridine core **4**, of these molecules is highlighted in Figure 1. A major drawback of

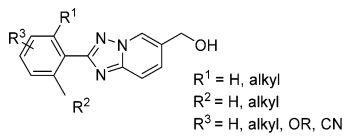


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Figure 1. 1,2,4-Triazole fragment of potential activators of GPR 40 for treatment of type 2 diabetes.

the described route (Scheme 1) was the requirement for a high-energy electrophilic-aminating agent, *O*-mesitylsulfonylhydroxylamine (MSH) to synthesize key intermediate **5**. Even though the preparation and safe use of MSH has been demonstrated,[27]

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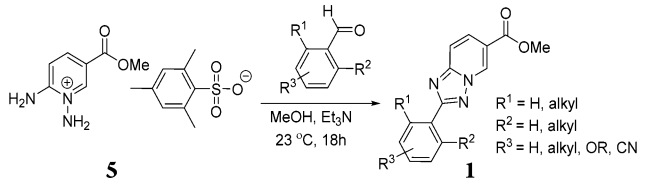
Scheme 1. Synthesis of 1 from MSH Intermediates



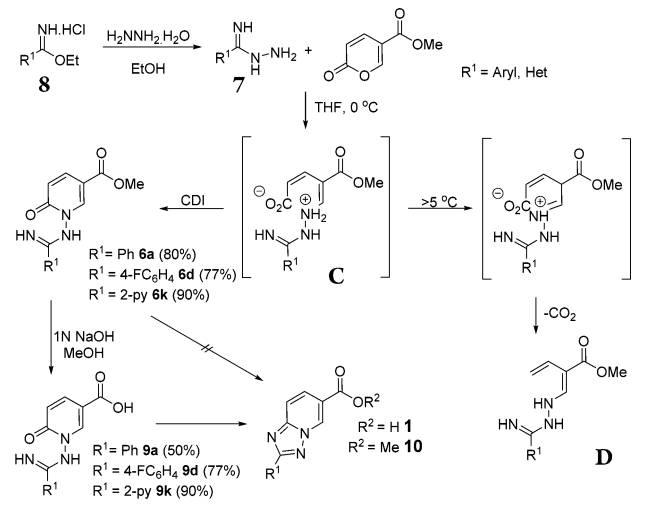
the desire remained to move away from this method of synthesis.

We envisioned that methyl coumalate **B**,[28] a renewable feedstock ultimately derived from glucose[29] via malic acid could be reacted with hydrazides to access the pyridine ring via a pyridine species and facilitate the cyclization to afford the 1,2,4-triazole ring without the requirement for oxidative N−N bond formation. Presently, we disclose two complementary metal-free synthetic routes to 6-methyl carboxylate-substituted *s*-[1,2,4]triazolo[1,5-*a*]pyridine systems previously unknown in the literature.

2.0. RESULTS AND DISCUSSION

In the course of synthetic route investigations carried out by our laboratories, a number of known methods were attempted to access the desired substituted 1,2,4- triazole core **4**. Several methods involving oxidative N−N bond formation performed poorly or failed completely at the cyclization stage when applied to the substrates required for our work.[21,30,31] Bearing this in mind, it was hoped that methyl coumalate **B** could be used as a platform chemical, reducing the overall chemical processing involved and providing a greener and more sustainable route to the biologically important pharmacophores discussed in this work. Scheme 2 details our initial strategy

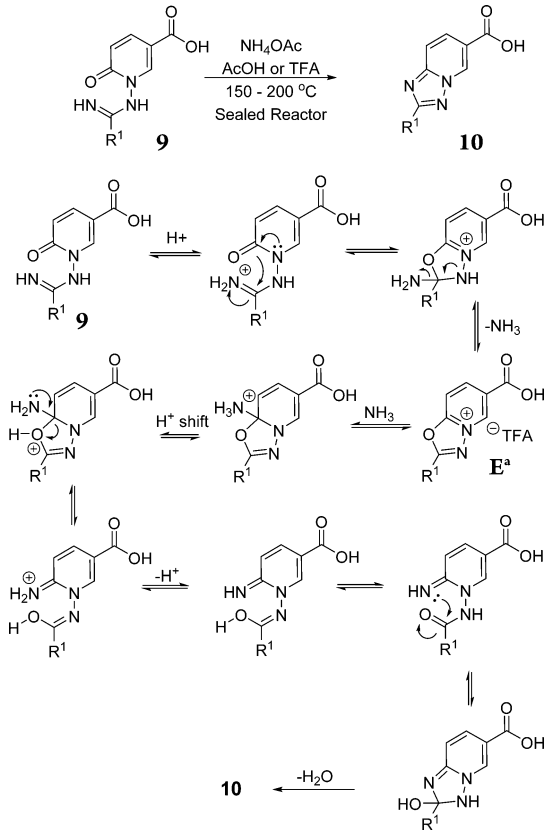
Scheme 2. Initial Efforts to *s*-[1,2,4]Triazolo[1,5-*a*]pyridine Ring System



using imidohydrazide pyridine (IHP) derivatives **6**, planned as potential intermediates for condensation to the 1,2,4-triazole system **1**.

A range of iminohydrazides **7** were prepared using the methods described by Pinner[32] from the corresponding nitriles via reaction of the Pinner salt **8** with hydrazine.[33] Preparation of the iminohydrazide pyridine ester proceeded from a Michael addition via a zwitterionic intermediate **C** (Scheme 2) which was stable at 0 °C. Careful control of temperature was important, because rapid decarboxylation of the intermediate adducts **C** to **D** occurred above 5 °C. Treatment of intermediate **C** with CDI promotes cyclization to give IHP **6**. Unfortunately, a range of efforts to promote a subsequent ring closure of the IHP esters, **6** to **1**, were unsuccessful, as the ester moiety activated the molecule toward 1,4-addition. Conversion to the acid derivative **9** facilitated the cyclization to the desired ring system **10**, though isolation issues were associated with this route due to the acid functionality of **10** and use of acetic acid or trifluoroacetic acid as solvents. In an effort to promote cyclization to **10**, additives were screened in a sealed-reactor system at elevated temperature. The sealed system permitted heating beyond the solvent boiling point and ensured containment of ammonia. It was found that ammonium acetate was an effective additive, though its role in the reaction mechanism was unclear. Understanding was gained when LC−MS analysis of the crude reaction mixtures showed the major product of the reaction gave an m/z + 1 higher than anticipated when the reaction was carried out in TFA. Further investigation by NMR and high-resolution mass spectrometry indicated that the cyclization reactions were proceeding via an oxadiazolium cationic intermediate **E** (Scheme 3), initially displacing the imidohydrazide nitrogen instead of displacing the oxygen as desired.

Scheme 3. Proposed Mechanism of 1,2,4-Triazole Formation from IHP acids



[a]1-D and 2-D NMR provided in Supporting Information.

The intermediate **E** undergoes attack by ammonia, either ammonium acetate derived or from oxygen displaced ammonia. The proposed cyclization mechanism in TFA is outlined in Scheme 3. It is likely that when the reaction is carried out in acetic acid, the ion pair is insufficient to arrest the

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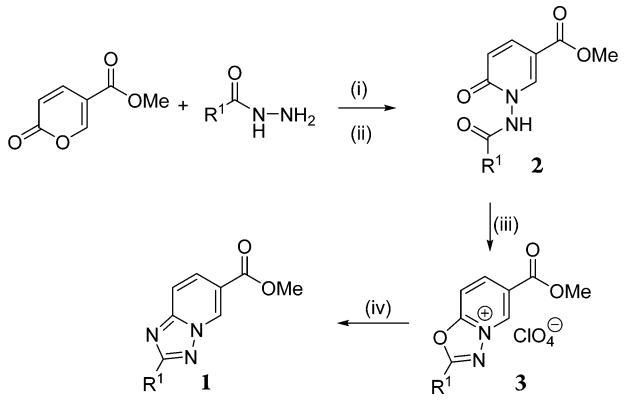
oxadiazolium **C**. Representative examples of prepared imidohydrazide esters **6** and acids **9** are provided in the experimental section for information purposes. Taking advantage of this mechanistic insight, the synthetic route was altered (Scheme 4)

Scheme 4. Revised Synthetic Route to the *s*-[1,2,4]Triazolo[1,5-*a*]pyridine Ring System[a]

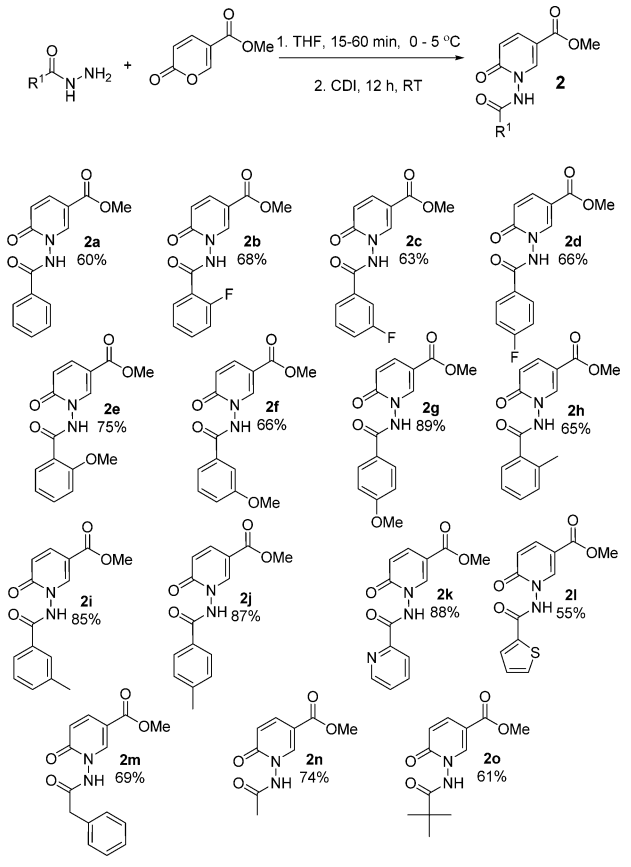


[a]Reagents and conditions: (i) THF, 0−5 °C, 15−60 min; (ii) CDI, 12 h, rt; (iii) 70% $HClO_4$, Ac_2O, < 35 °C; (iv) NH_4OAc, AcOH, 120 °C, 15−90 min.

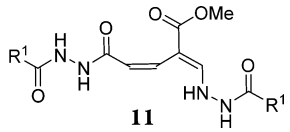
to proceed directly through the oxadiazolium, shortening the synthesis by 1−2 steps depending on the aromatic -substitution pattern.

A series of novel dihydrazides of type **2** (Scheme 5) were prepared through sequential treatment of a methyl coumalate/THF solution, with the corresponding commercially available hydrazide followed by CDI, in good to excellent yield (40−89%). Initial addition to methyl coumalate was complete in under 2 h in all cases. After addition of CDI, cyclization was complete in 3−8 h, though the reactions were frequently left overnight. The addition and cyclization reactions were conducted at 0−5 °C to avoid the decarboxylation encountered previously at the zwitterion stage.

Scheme 5. Dihydrazide Synthesis Substrate Scope



After workup, if desired, dihydrazides **2** could be used crude in the next synthetic step. Use of 1 N HCl in the workup resulted in the removal of the major impurity from the crude material, residual imidazole. Dihyrazides (**2g**, **2i**−**k**) precipitated following cyclization with CDI, required no workup, and lead to increased isolated yields (55−89%). The reaction also proceeds with EtOAc or CH_3CN as the reaction solvent and this leads to more instances of product precipitation, though yields are lower by 5−10%.



An impurity commonly observed by LC−MS was the double addition products **11**, likely derived from an initial 1,2-addition of **A** and **B**. These species were rejected in the workup and could be kept to a minimum through use of a slight excess of methyl coumalate, which was utilized as a dilute solution when added to the hydrazide starting material. Alkyl derivative **2n** required storage under moisture free conditions, because of the acetate being labile to hydrolysis.

Tetrafluoroborate and perchlorate quaternary salts of simple 1,3,4-oxadiazoles were first described by Boyd[34] in 1967 and were noted to be very sensitive to nucleophilic attack, particularly by water. A diazapine synthesis utilizing an oxadiazolium perchlorate intermediate noted the strict requirement for dry reaction conditions due to their reactivity with even poor nucleophiles.[35]

A selection of novel oxadiazolium perchlorate salts **3** were prepared through the action of 1.5−5 equiv of aq 70% perchloric acid on a slurry of the dihydrazides **2** in acetic anhydride (Scheme 6). The rate of perchloric acid addition was such that the temperature was not allowed to exceed 35 °C, with the slurry becoming a solution after addition of 1.5 equiv of acid. Salts **3**, containing aromatic substituents, showed particular stability to water. In fact, the isolation of the 2-aryl perchlorate salts could be accomplished through slowly pouring the reaction mixture into cold water (5−10 °C) and then with subsequent separation of the perchlorate salts by filtration. The hydrolytic stability was investigated through exposure of **3d** to 30 volumes of water at ambient temperature for 5 days and resulted in no loss of salt potency. Isolated yields of the perchlorate salts were in the range of 62−87% and were identified by the absence of the N−H signal in their ^1H NMR spectra, and the presence of their stable cations were observable by mass spectrometry. Analysis of the infrared spectra showed C=N$^+$ and C=N stretches at 1640 and 1610 cm^{-1}, and characteristic perchlorate stretches[36] were observed at 1090 cm^{-1}. The intact structure of the perchlorate salt was firmly established by X-ray crystallographic analysis. The unit cell was composed of a 1:1 oxadiazolium/perchlorate salt, and no solvent or water was detected in the crystal (Scheme 6, **3d**).

Oxadiazolium perchlorates, **3a**−**j**, **l** appear to be the only examples of compounds of this type with this degree of water stability under ambient conditions. This affords them greater

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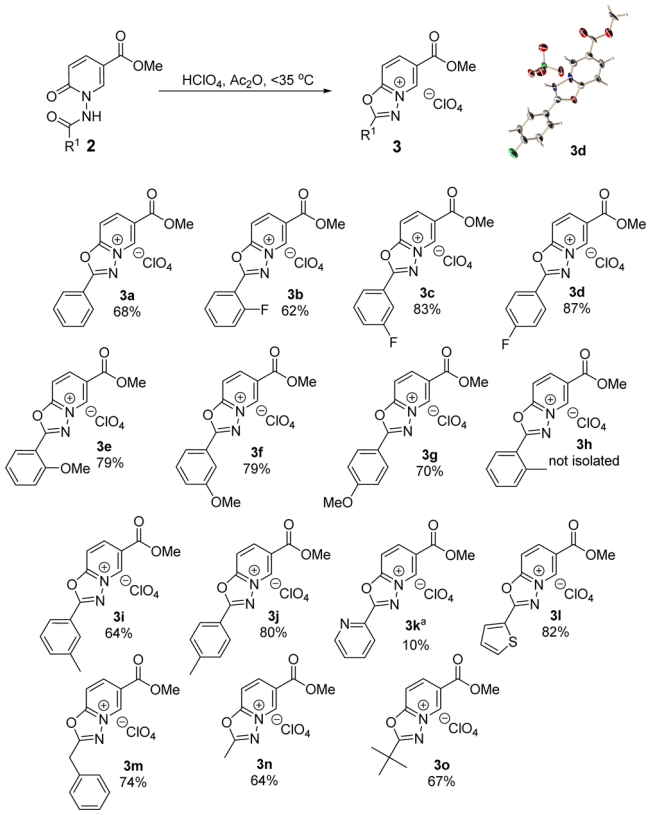
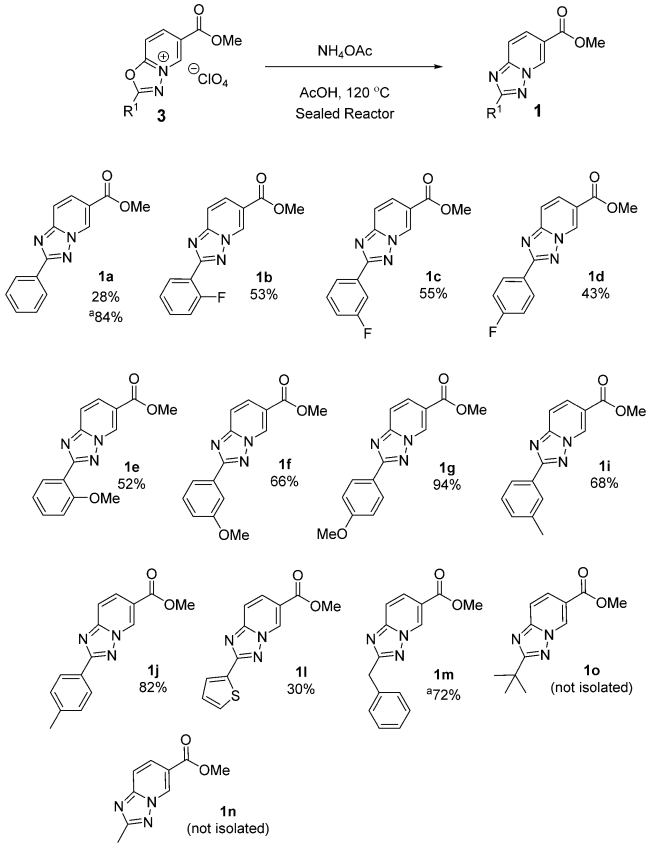
Scheme 6. Perchlorate Salt Substrate Scope



[a]After 36 h, not isolated.

Scheme 7. Synthetic Strategy Toward *s*-[1,2,4]Triazolo[1,5-*a*]pyridine Ring System



[a]Ac_2O (3 equiv), 130 °C.

synthetic utility than the literature examples because of their relative ease of use and stability. When R^1 = benzyl or alkyl, isolation was achieved through trituration with cold MTBE, though hydrolytic instability (2−5 °C) was not observed. Difficulties were encountered in the preparation of a 2-pyridyl derivative **3k**, as low conversion (~10%) to the oxadiazolium was observed by LC−MS even after long reaction times (36 h). Evidence for the formation of *o*-tolyl derivative **3h** was obtained by LC−MS and HRMS, but all attempts at isolation were unsuccessful. Perchlorate **3n** showed substantially less thermal stability than other analogues in this series, decomposing above 100 °C.

The perchlorate salts, **3**, were combined with ammonium acetate in hot acetic acid in a sealed reactor to yield the desired products in moderate to excellent yields in 15−90 min (Scheme 7). Despite the aforementioned hydrolytic stability of perchlorates **3**, under ambient conditions, cyclization of the prepared oxadiazolium salts **3** to the bicyclic triazoles **1** was sensitive to water ascribed to the reaction temperatures involved (120 °C). The presence of water in the reaction, through association with reagents, moisture in the system, or from the resulting cyclization condensation, leads to a competing hydrolysis returning oxadiazolium salts, **3**, to the dihydrazides **2**. The use of molecular sieves gave minor improvements in yield, but water trapping was possibly poor owing to the presence of relatively large quantities of ammonium, swamping the ability of the sieves to store water.[37] Addition of 2−4 equiv of acetic anhydride as a water scavenger achieved a substantial improvement in product yield (~55% for **1a**). Even without the addition of acetic anhydride, the isolated yield of **1g** was near quantitative, and the highest yields in the series were observed when R^1 was electron rich.

The isolation of the triazole products **1a−l** was relatively straightforward as the presence of the ester greatly facilitated isolation and purification relative to their acid derivatives **10**. Simple cooling of the reaction mixture postreaction to 5−10 °C, and addition of cold water (2−5 °C) resulted in precipitation of the desired products with complete rejection of impurities into the mother liquor. Triazole **1m** was triturated with cold MTBE to isolate. Alkyl derivatives **1n** and **1o** were successfully synthesized; however, attempts to isolate **1n** were hampered by its general instability. Reactions to produce **1o** resulted in poor yields with significant quantities of dihydrazide **2o** present, even with the addition of acetic anhydride.

3.0. CONCLUSIONS

In summary, a cost-effective synthesis of novel s-[1,2,4]triazolo-[1,5-*a*]pyridine **1** compounds from methyl coumalate and commercially available hydrazides has been accomplished in three linear steps by a chromatography-free process. Our new synthetic strategy, using methyl coumalate as the primary starting material, provides a useful alternative to literature methods and is particularly effective for the synthesis of aryl-substituted derivatives. The synthesis is metal free, shows good substrate scope, and initial pyridine dihydrazide **2** generation removes the requirement for N−N bond formation in the strategy. Additionally, the oxadiazolium perchlorate salts generated in the course of the synthesis are unusually water stable and may be stored for many months without any sign of degradation.

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4.0. EXPERIMENTAL SECTION

General. All reagents were reagent grade, obtained from commercial suppliers and used without further purification. All solvents were HPLC grade and used as supplied. Reaction monitoring was accomplished by TLC or LC−MS using an Agilent 6130 Quadropole LC−MS fitted with a photo diode array detection and an XBridge C18 2.5 μm, 1.0 × 75 mm column at 30 °C. TLC plates were visualized under UV light (254 nm). Flash chromatography was carried out with silica gel 60 (230−400 ASTM mesh) on a Teledyne Isco CombiFlash Rf+ PurIon with hexane/ethyl acetate as the solvent gradient system. ^{1}H and ^{13}C NMR spectra were obtained on a Varian spectrometer at 400 and 100 MHz, respectively. Proton fine splitting reported as follows: (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, dd = doublet of doublets, dt = doublet of triplets). Chemical shifts were referenced on residual solvent peaks: $CDCl_3$ (δ = 7.26 ppm for ^{1}H NMR and 77.00 ppm for ^{13}C NMR), DMSO $(CD_3)_2SO$ (δ = 3.33 ppm for ^{1}H NMR and 39.51 ppm for ^{13}C NMR). Structural assignment of resonances have been performed with the help of 2D NMR gradients experiments (COSY, multiplicity edited ^{1}H−^{13}C HSQC, ^{1}H−^{13}C HMBC, and ^{1}H−^{15}N HMBC. High-resolution mass spectra were measured on a Thermo Scientific LTQ-Orbitrap Discovery using electrospray ionization mode (ESI+) with a mass accuracy greater than 2 ppm, and an applied mass range from 75 to 1500 Da. IR spectra (4000−400 cm^{-1}) were collected and performed by ATR-FTIR (Attenuated Total Reflectance) on a Nicolet 6700 FT-IR with a Smart OMNI sampler on neat solid samples. DSC was performed on a TA SA+ Discovery series instrument running TRIOS Explorer software (10 °C/min).

General Procedures. *General Procedure for Products **6a,d and k**.* To a solution of methyl-6-oxopyran-3-carboxylate (6.79 g, 44 mmol) in THF (60 mL) at 0 °C under a nitrogen atmosphere was added a solution of the appropriate imidohydrazide **7** (44 mmol) in THF (48 mL) via cannula over 5 min. The mixture was stirred until complete consumption of the methyl coumalate occurred, which was indicated by TLC or LC−MS (< 2 h). 1,1′-Carbonyldiimidazole was added, with the solution proceeding through a number of color changes to eventually yield a black solution, which was slowly allowed to warm to room temperature overnight. The reaction mixture was diluted with EtOAc (50 mL) and transferred to a separator funnel. It was washed with water (3 × 70 mL), brine (50 mL), dried with sodium sulfate, and concentrated by rotary evaporation to yield a brown solid which was used without further purification in the production of **9**.

*General Procedure for Products **9a,d and k**.* To a suspension of **6** (3.6 mmol) in methanol (5 mL) was added 4 mL 1N aq NaOH (4 mmol, 1.1 equiv). The mixture was allowed to stir until LC−MS/TLC analysis indicated the complete consumption of the starting material. The reaction slowly became homogeneous as it progressed. When the reaction was complete, the solution was acidified to pH 4 with saturated aq citric acid. A white precipitate formed, which was isolated by filtration and washed with water (2 × 5 mL)

*Procedure for Synthesis of Oxadiazolium Intermediate **E** (R = 4-F C_6H_4).* A solution of **9d** (20 mg (0.07 mmol) and ammonium acetate (27 mg, 0.35 mmol, 5 equiv) in TFA-d_1 (0.75 mL) was placed in a 2 mL Hastelloy port-connector reactor and placed inside a modified GC oven. The reaction was heated at 200 °C for 2 h, cooled to room temperature, and the full contents of the reactor were analyzed by NMR spectroscopy.

*General Procedure for Products **2a−o**.* To a suspension of the appropriate hydrazide (16.4 mmol, 1.1 equiv) in THF (20 mL) at 0 °C under a nitrogen atmosphere was added a solution of methyl-6-oxopyran-3-carboxylate (2.3 g, 15 mmol) in THF (20 mL), dropwise over 10−30 min. The mixture was stirred until complete consumption of the methyl coumalate occurred, which was indicated by TLC or LC−MS (15−60 min). 1,1′-Carbonyldiimidazole (21.3 mmol, 1.3 equiv) was added, with the solution proceeding through a number of color changes to eventually yield a black solution which was slowly allowed to warm to room temperature overnight. The reaction mixture was diluted with EtOAc (50 mL) and transferred to a separator funnel. It was washed with 1 N HCl (2 × 30 mL), water (40 mL), brine (40 mL), dried with sodium sulfate, and concentrated by rotary evaporation to yield a brown solid. The products could be forward processed in their crude form for use in the oxadiazolium synthesis. Isolated yields were determined on analytically pure samples, if required, after the product was isolated as a white solid by column chromatography using hexane/ethyl acetate (40:60) as eluents.

*General Procedure for Products **3a−o**.* A suspension of dihydrazide (**1a−o**) (3 mmol) in acetic anhydride (6 mL) was cooled on an ice bath and purged with nitrogen. A 70% perchloric acid solution (9 mmol, 1.5−5 equiv) was added dropwise at such a rate that the temperature of the reaction mixture never exceeded 35 °C. Upon acid addition, the contents of the reaction pot slowly went into solution. After complete acid addition, the reaction was removed from the ice bath and allowed to stir for 1−2 h until complete consumption of the starting material was indicated by TLC or LC−MS. The reaction mixture (**3a−j, l**)was slowly poured into water (20 mL), and the resulting crystals were filtered and washed with water (2 × 5 mL). Compounds **3m−o** were isolated by trituration with MTBE (10 mL), filtration, and washing with cold ether (5 mL). The solids were dried in a vacuum oven at 35 °C and used without further purification.

*General Procedure for Products **1a−o**.* A mixture of oxadiazolium perchlorate salt (1 mmol) (**3a−o**) and ammonium acetate (3.5−5 equiv) was dissolved in acetic acid (2.5 mL) in a 20 mL thick-walled screw-capped tube, flushed with nitrogen and heated to 120 °C for 15−90 min. The reaction was monitored by LC−MS and deemed complete when the dihydrazide **2** was consumed. The tube was cooled to room temperature and the contents slowly poured into 20 mL of water (5−10 °C). The desired triazole was isolated as a solid by filtration and the solids washed with water (2 × 10 mL). Where noted, 2−4 equiv of acetic anhydride was also added to the reaction in order to suppress hydrolysis of **3** to **2**.

*Methyl 1-Benzamido-6-oxo-1,6-dihydropyridine-3-carboxylate (**2a**).* White solid: Yield: 8.46 g (60%); mp (DSC) (10 °C/min) onset 183.42 °C, maximum 183.86 °C; IR (ATR) ν_{max} 3259, 1720, 1687, 1668, 1604, 1528, 1492, 1447, 1314, 1293, 1266, 1120, 1108 cm^{-1};^{1}H NMR (400 MHz, DMSO) δ_H: 3.79 (s, 3H), 6.63 (d, J = 9.6 Hz, 2H), 7.56 (m, 2H), 7.66, (m, 1H), 7.93 (m, 3H), 8.48 (d, J = 2.4 Hz, 1H), 11.85 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ_C: 52.5, 109.1, 120.2, 128.3, 129.1, 131.7, 133.1, 139.5, 146.7, 159.9, 164.3, 166.4; *m/z* 271.1; HRMS (ESI) calcd for $C_{14}H_{13}N_2O_4$ [M+H$^+$] 273.0870, found 273.0871.

*Methyl 1-(2-Fluorobenzamido)-6-oxo-1,6-dihydropyridine-3-carboxylate (**2b**).* White solid: Yield 1.30 g (68%); mp (DSC) (10 °C/min) onset 129.41 °C, maximum 132.10 °C; IR (ATR) ν_{max} 3177, 1719, 1660, 1614, 1541, 1447, 1316, 1279, 1260, 1122, cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ_H: 3.79 (s, 3H), 6.64 (d, J = 10 Hz, 1H), 7.37 (m, 2H), 7.64 (m, 1H), 7.87 (m, 2H), 8.49 (d, J = 2.4 Hz, 1H), 11.71 (brs, 1H); ^{19}F δ_F: −112.1; ^{13}C NMR (100 MHz, DMSO) δ_C: 52.5, 109.1, 116.9 (d, J = 21 Hz), 120.3, 120.9 (d, J = 14 Hz) 125.1, 131.1, 134.5 (d, J = 7.2 Hz), 139.5, 146.5, 159.7, 160.1 (d, J = 252 Hz), 163.7, 164.2; *m/z* 291.1; HRMS (ESI) calcd for $C_{14}H_{12}N_2O_4F$ [M+H$^+$] 291.0776, found 291.0779.

*Methyl 1-(3-Fluorobenzamido)-6-oxo-1,6-dihydropyridine-3-carboxylate (**2c**).* White solid: Yield 1.27 g (63%); mp (DSC) (10 °C/min) onset 188.85 °C, maximum 190.27 °C; IR (ATR) ν_{max} 3186, 1723, 1696, 1658, 1608, 1591, 1445, 1311, 1283, 1263, 1208, 1124 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ_H: 3.79 (s, 3H), 6.64 (d, J = 9.6 Hz, 1H), 7.51 (td, J = 6.4 Hz, 2.4 Hz, 1H), 7.62 (q, J = 8 Hz, 1H), 7.73 (d, J = 9.6 Hz, 1H), 7.79 (d, J = 6.8 Hz, 1H), 7.89, (dd, J = 7.2, 2.4 Hz, 1H), 8.52 (d, J= 2.4 Hz, 1H), 11.98 (br s, 1H); ^{19}F δ_F: −112.1; ^{13}C NMR (100 MHz, DMSO) δ_C: 52.5, 109.2, 115.1 (d, J = 24 Hz), 120.1 (d, J = 21 Hz), 120.3, 124.5 (d, J= 3 Hz), 131.4 (d, J = 8 Hz), 134.0 (d, J = 8 Hz, 139.5, 146.6, 159.8, 162.5 (d, J = 245 Hz), 164.2, 165.2 (d, J= 3 Hz); *m/z* 291.1; HRMS (ESI) calcd for $C_{14}H_{12}N_2O_4F$ [M+H$^+$] 291.0776, found 291.0779

*Methyl 1-(4-Fluorobenzamido)-6-oxo-1,6-dihydropyridine-3-carboxylate (**2d**).* White solid: Yield 0.95 g (66%); mp (DSC) (10 °C/min) onset 260.04 °C, maximum 260.31 °C; IR (ATR) ν_{max} 3242, 1718, 1680, 1660, 1603, 1535, 1502, 1446, 1294, 1263, 1223, 1129, 1114 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ_H: 3.79 (s, 3H), 6.65 (d, J = 9.6 Hz, 1H),

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J. Org. Chem. 2017, 82, 6279−6288

7.41 (t, J = 8.8 Hz, 2H), 7.90 (dd, J = 2.4, 9.6 Hz, 1H), 8.02 (m, 2H), 8.50 (d, J = 2.4 Hz, 1H); ^{19}F δ_F: −106.8; ^{13}C NMR (100 MHz, DMSO) δ_C: 52.5, 109.1, 116.2 (d, J = 24 Hz), 120.2, 128.3, 131.1, 131.2, 139.5, 146.7, 160.0, 164.2, 165.5; *m/z* 291.1; HRMS (ESI) calcd for $C_{14}H_{12}N_2O_4F$ [M+H$^+$] 291.0776, found 291.0782.

*Methyl 1-(2-Methoxybenzamido)-6-oxo-1,6-dihydropyridine-3-carboxylate (**2e**).* White solid: Yield 2.5 g (75%); mp (DSC) (10 °C/min) onset 130.24 °C, maximum 139.42 °C; IR (ATR) ν_{max} 3278, 1710, 1697, 1675, 1602, 1500, 1477, 1452, 1317, 1301, 1275, 1117, 1104, 1015 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ_H: 3.78 (s, 3H), 3.92 (s, 3H), 6.61, (d, J = 10 Hz, 1H), 7.08 (m, 1H), 7.30 (m, 1H), 7.59 (m, 1H), 7.87 (m, 2H), 8.35 (d, J = 2.4 Hz, 1H), 11.16 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ_C: 52.5, 56.5, 108.7, 112.8, 119.9, 120.3, 121.1, 131.5, 133.4, 139.2, 146.7, 158.1, 159.7 164.3, 164.9; *m/z* 303.1; HRMS (ESI) calcd for $C_{15}H_{15}N_2O_5$ [M+H$^+$] 303.0975, found 303.0979.

*Methyl 1-(3-Methoxybenzamido)-6-oxo-1,6-dihydropyridine-3-carboxylate (**2f**).* White solid: Yield 2.2 g (66%); mp (DSC) (10 °C/min) onset 186.65 °C, maximum 186.87 °C; IR (ATR) ν_{max} 3234, 1720, 1670, 1661, 1597, 1527, 1490, 1444, 1304, 1293, 1275, 1233, 1120, 1035 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ_H: 3.78 (s, 3H), 3.82, (s, 3H), 6.63, (d, J = 9.2 Hz, 1H), 7.20 (dd, J = 2.4, 5.6 Hz, 1H), 7.49 (m, 3H), 7.89 (dd, J = 2.4, 9.6 Hz, 1H), 8.48 (d, J = 2.4 Hz, 1H), 11.94 (br s, 1H); ^{13}C NMR (100 MHz, DMSO) δ_C: 52.5, 55.8, 109.1, 113.3, 119.0, 120.2, 120.5, 130.0, 133.0, 139.5, 146.7, 159.7, 159.9, 164.2, 166.2; *m/z* 303.1; HRMS (ESI) calcd for $C_{15}H_{15}N_2O_5$ [M+H$^+$] 303.0975, found 303.0982.

*Methyl 1-(4-Methoxybenzamido)-6-oxo-1,6-dihydropyridine-3-carboxylate (**2g**).* Isolated by filtration, no workup. White solid: Yield 4.0 g (89%); mp (DSC) (10 °C/min) onset 193.02 °C, maximum 193.72 °C; IR (ATR) ν_{max} 3219, 1722, 1679, 1659, 1606, 1535, 1507, 1445, 1312, 1295, 1271, 1253, 1196, 1128, 1105, 1025 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ_H: 3.78 (s, 3H), 3.84 (s, 3H), 6.62 (d, J = 9.6 Hz, 1H), 7.09 (d, J = 9.6 Hz, 2H), 7.90 (m, 3H), 7.43 (d, J = 2.4 Hz, 1H), 11.69 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ_C: 52.5, 56.0, 109.0, 114.4, 120.2, 123.7, 130.3, 139.4, 146.9, 160.1, 163.1, 164.3, 166.0; *m/z* 303.1; HRMS (ESI) calcd for $C_{15}H_{15}N_2O_5$ [M+H$^+$] 303.0975, found 303.0982

*Methyl 1-(2-Methylbenzamido)-6-oxo-1,6-dihydropyridine-3-carboxylate (**2h**).* White solid: Yield 2.30 g (65%); mp (DSC) (10 °C/min) onset 166.41 °C, maximum 169.01 °C; IR (ATR) ν_{max} 3209, 1724, 1684, 1663, 1603, 1544, 1513, 1444, 1311, 1286, 1259, 1121, 1101 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ_H: 2.41 (s, 3H), 3.80 (s, 3H), 6.62 (d, J = 9.6 Hz, 1H), 7.31 (m, 2H), 7.44 (m, 1H), 7.65 (m, 1H), 7.88 (dd, J = 9.2, 2.4 Hz, 1H), 8.52 (d, J= 2.4 Hz, 1H), 11.60 (br s, 1H); ^{13}C NMR (100 MHz, DMSO) δ_C: 19.7, 52.5, 109.0, 120.3, 126.0, 128.4, 131.1, 131.2, 133.5, 136.9, 139.5, 146.7, 159.8, 164.3, 168.7; *m/z* 287.1; HRMS (ESI) calcd for $C_{15}H_{15}N_2O_4$ [M+H$^+$] 287.1026, found 287.1032

*Methyl 1-(3-Methylbenzamido)-6-oxo-1,6-dihydropyridine-3-carboxylate (**2i**).* White solid. Isolated by filtration, no workup: Yield 3.30 g (85%); mp (DSC) (10 °C/min) onset 175.59 °C, maximum 177.84 °C; IR (ATR) ν_{max} 3176, 1724, 1702, 1660, 1607, 1533, 1443, 1311, 1268, 1125, 1106, 1069 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ_H: 2.38 (s, 3H), 3.78 (s, 3H), 6.63 (d, J = 9.6 Hz, 1H), 7.45 (m, 2H), 7.75 (m, 2H), 7.88 (dd, J = 2.4, 9.2 Hz, 1H), 8.46 (d, J = 2.4 Hz, 1H), 11.80 (br s, 1H); ^{13}C NMR (100 MHz, DMSO) δ_C: 21.3, 52.5, 109.1, 120.2, 125.4, 128.8, 129.0, 131.7, 133.7, 138.5, 139.4, 146.7, 159.92, 164.2, 166.6; *m/z* 287.1; HRMS (ESI) calcd for $C_{15}H_{15}N_2O_4$ [M+H$^+$] 287.1026, found 287.1031.

*Methyl 1-(4-Methylbenzamido)-6-oxo-1,6-dihydropyridine-3-carboxylate (**2j**).* White solid. Isolated by filtration, no workup: Yield 5.15 g (87%); mp (DSC) (10 °C/min) onset 192.50 °C, maximum 193.74 °C; IR (ATR) ν_{max} 3210, 1701, 1663, 1610, 1531, 1503, 1445, 1315, 1288, 1270, 1122 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ_H: 2.38 (s, 3H), 3.78 (s, 3H), 6.63 (d, J = 9.6 Hz, 1H), 7.35 (d, J = 8 Hz, 2H), 7.85 (m, 3H), 8.45 (d, J = 2 Hz, 1H), 11.77 (br s, 1H); ^{13}C NMR (100 MHz, DMSO) δ_C: 21.5, 52.5, 109.1, 120.2, 128.3, 129.6, 139.4, 143.3, 146.8, 159.9, 164.25, 166.35; *m/z* 287.1; HRMS (ESI) calcd for $C_{15}H_{15}N_2O_4$ [M+H$^+$] 287.1026, found 287.1031.

*Methyl 6-Oxo-1-(picolinamido)-1,6-dihydropyridine-3-carboxylate (**2k**).* White solid. Isolated by filtration, no workup: Yield 3.4 g (87%); mp (DSC) (10 °C/min) onset 222.11 °C, maximum 222.76 °C; IR (ATR) ν_{max} 3301, 1727, 1712, 1682, 1543, 1483, 1443, 1317, 1295, 1281, 1103, 999 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ_H: 3.78 (s, 3H), 6.61 (d, J = 9.6 Hz, 1H), 7.72 (m, 1H), 7.87 (dd, J = 9.6 Hz, 2.8 Hz, 1H), 8.07 (m, 2H), 8.41 (d, J = 2.4 Hz, 1H), 8.74 (d, J = 4.4 Hz, 1H), 11.95 (br s, 1H); ^{13}C NMR (100 MHz, DMSO) δ_C: 52.5, 109.0, 120.3, 123.3, 128.2, 138.5, 139.3, 146.7, 148.4, 149.3, 159.6, 163.8, 164.2; *m/z* 275.1; HRMS (ESI) calcd for $C_{13}H_{12}N_3O_4$ [M+H$^+$] 274.0822, found 274.0828

*Methyl 6-Oxo-1-(thiophene-2- carboxamido)-1,6-dihydropyridine-3-carboxylate (**2l**).* White solid: Yield 1.69 g (55%); mp (DSC) (10 °C/min) onset 239.60 °C, maximum 239.88 °C; IR (ATR) ν_{max} 3226, 3096, 1715, 1660, 1610, 1536, 1512, 1443, 1419, 1357, 1314, 1272, 1121, 882, 859 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ_H: 3.78 (s, 3H), 6.63 (d, J = 10 Hz, 1H), 7.26, (t, J = 4 Hz, 1H), 7.89 (m, 1H), 7.95 (m, 2H), 8.46 (d, J = 2 Hz, 1H), 11.91 (br s, 1H); ^{13}C NMR (100 MHz, DMSO) δ_C: 52.5, 109.2, 120.2, 128.8, 131.0, 133.5, 135.9, 139.6, 146.7, 159.9, 161.4, 164.2; *m/z* 279.0; HRMS (ESI) calcd for $C_{12}H_{11}N_2O_4S$ [M+H$^+$] 279.0434, found 274.0439.

*Methyl 6-Oxo-1-(2-phenylacetamido)-1,6-dihydropyridine-3-carboxylate (**2m**).* White solid: Yield 6.64 g (69%); mp (DSC) (10 °C/min) onset 107.26 °C, maximum 109.70 °C.; IR (ATR) ν_{max} 3147, 2949, 1720, 1663, 1604, 1540, 1513, 1495, 1443, 1309, 1278, 1134, 1112, 1097 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.67 (s, 2H), 3.76 (s, 3H), 6.58 (d, J = 10 Hz, 1H), 7.33 (m, 5H), 7.85 (m, 1H), 8.25 (d, J = 2.4 Hz, 1H), 11.59 (s, 1H); ^{13}C NMR (100 MHz, DMSO). δ_C: 39.3, 52.5, 108.9, 120.2, 127.2, 128.8, 129.7, 135.1, 139.3, 146.3, 159.7, 164.2, 170.5; *m/z* 287.1; HRMS (ESI) calcd for $C_{15}H_{15}N_2O_4$ [M+H$^+$] 287.1026, found 287.1032.

*Methyl 1-Acetamido-6-oxo-1,6-dihydropyridine-3-carboxylate (**2n**).* White solid: Yield 6.64 g (69%); mp (DSC) (10 °C/min) 133 °C (decomposes); IR (ATR) ν_{max} 3210, 3031, 1726, 1672, 1612, 1540, 1450, 1375, 1313, 1289, 1261, 1117, 1098 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.20 (s, 3H), 3.85 (s, 3H), 6.64 (d, J = 9.6 Hz, 1H), 7.95 (dd, J = 2.8, 9.2 Hz), 8.22 (d, J = 2.0 Hz, 1H), 10.12 (s, 1H); ^{13}C NMR (100 MHz, DMSO). δ_C: 20.9, 52.3, 110.5, 119.6, 140.0, 144.5, 160.6, 163.9, 170.2. *m/z* 211.1; HRMS (ESI) calcd for $C_9H_{11}N_2O_4$ [M+H$^+$] 211.0713, found 211.0718.

*Methyl 6-Oxo-1-pivalamido-1,6-dihydropyridine-3-carboxylate (**2o**).* White solid: Yield 4.58 g (61%); mp (DSC) (10 °C/min) onset 159.47 °C, maximum 159.60 °C; IR (ATR) ν_{max} 3270, 1719, 1669, 1536, 1497, 1443, 1309, 1284, 1225, 1139, 1113, 915 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ_H: 1.21 (s, 9H), 3.77 (s, 3H), 6.56 (d, J = 9.6 Hz, 1H), 7.83 (m, 1H), 8.21 (d, J = 2 Hz, 1H), 10.90 (br s, 1H); ^{13}C NMR (100 MHz, DMSO) δ_C: 27.3, 38.4, 52.5, 108.8, 120.2, 139.3, 146.8, 159.8, 164.3, 177.7; *m/z* 253.1; HRMS (ESI) calcd for $C_{12}H_{17}N_2O_4$ [M+H$^+$] 253.1183, found 253.1187.

*Methyl 2-Phenyl-4λ^4-[1,3,4]oxadiazolo[3,2-a]pyridine-6-carboxylate perchlorate (**3a**).* Off-white solid: Yield 1.53 g (68%); mp (DSC) (10 °C/min) onset 265.21 °C, maximum 267.87 °C; IR (ATR) ν_{max} 3112, 1729, 1646, 1610, 1567, 1452, 1437, 1302, 1286, 1209, 1089 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ_H: 4.01 (s, 3H), 7.81 (m, 2H), 7.93, (m, 1H), 8.28 (d, J = 7.6 Hz, 2H), 8.83 (d, J = 9.2 Hz), 9.12 (d, J = 9.2 Hz, 1H), 10.35 (s, 1H); ^{13}C NMR (100 MHz, DMSO δ_C: 54.2, 112.0, 120.1, 126.3, 128.9, 130.8, 135.7, 136.3, 144.7, 155.2, 162.4, 166.0; *m/z* 255.1; HRMS (ESI) calcd for $C_{14}H_{11}N_2O_3$ [M$^+$] 255.0764, found 255.0766.

*Methyl 2-(2-Fluorophenyl)-4λ^4-[1,3,4]oxadiazolo[3,2-a]pyridine-6-carboxylate perchlorate (**3b**).* Off-white solid: Yield 0.95 g (62%); mp (DSC) (10 °C/min) 205 °C (decomposes); IR (ATR) ν_{max} 3088, 1744, 1641, 1625, 1597, 1484, 1462, 1308, 1290, 1089 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ_H: 4.02 (s, 3H), 7.66 (t, J = 8 Hz, 1H), 7.72 (t, J = 10.8 Hz, 1H), 8.00 (q, J = 6 Hz, 1H), 8.30 (t, J = 7.6 Hz, 1H), 8.88 (d, J = 9.2 Hz, 1H), 9.15 (d, J = 9 Hz, 1H); ^{19}F δ_F: −106.6; ^{13}C NMR (100 MHz, DMSO δ_C: 54.2, 108.8 (d, J = 11 Hz), 112.0, 118.4 (d, J = 20 Hz), 126.4, 126.8 (d, J = 3 Hz), 131.2, 135.8, 138.8 (d, J = 2 Hz) 145.1, 154.7, 161.0 d, J = 261 Hz), 162.4, 162.8 (d, J= 6 Hz); *m/z* 273.1; HRMS (ESI) calcd for $C_{14}H_{10}N_2O_3F$ [M$^+$] 273.0670, found 273.0673.

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*Methyl 2-(3-Fluorophenyl)-4λ⁴-[1,3,4]oxadiazolo[3,2-a]pyridine-6-carboxylate perchlorate (**3c**).* Off-white solid: Yield 0.65 g (83%); mp (DSC) (10 °C/min) onset 257.26 °C, maximum 258.12 °C; IR (ATR) ν_{max} 3091, 1733, 1646, 1438, 1288, 1255, 1092 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ_H: 4.01 (s, 3H), 7.86 (m, 2H), 8.15 (m, 2H), 8.84 (d, J = 9.2 Hz, 1H), 9.15 (m, 1H), 10.38 (s, 1H); ^{19}F δ_F: −109.5; ^{13}C NMR (100 MHz, DMSO) δ_C: 54.2, 112.1, 115.5 (d, J = 24 Hz), 122.0 (d, J= 3 Hz), 123.4 (d, J = 26 Hz), 125.4, 126.5, 133.5 (d, J = 8 Hz), 135.8, 145.8, 155.1, 162.4, 162.7 (d, J = 248 Hz), 165.0; *m/z* 273.1; HRMS (ESI) calcd for $C_{14}H_{10}N_2O_3F$ $[M^+]$ 273.0670, found 273.0675.

*Methyl 2-(4-Fluorophenyl)-4λ⁴-[1,3,4]oxadiazolo[3,2-a]pyridine-6-carboxylate perchlorate (**3d**).* White solid: Yield 0.56 g (87%); mp (DSC) (10 °C/min) onset 250.22 °C, maximum 251.49 °C; IR (ATR) ν_{max} 3100, 1733, 1647, 1615, 1503, 1433, 1301, 1240, 1087 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ_H: 4.01 (s, 3H), 7.67 (t, J = 8.8 Hz, 2H), 8.37 (dd, J = 5.5, 8.4 Hz, 2H), 8.82 (d, J = 9.2 Hz, 1H), 9.12 (m, 1H), 10.35 (s, 1H); ^{19}F δ_F: −100.7; ^{13}C NMR (100 MHz, DMSO) δ_C: 54.2, 112.0, 116.8, 118.4 (d, J = 22 Hz), 119.7, 126.3, 132.1 (d, J = 8 Hz), 135.7, 144.8, 155.1, 162.4, 165.2; *m/z* 273.1; HRMS (ESI) calcd for $C_{14}H_{10}N_2O_3F$ $[M^+]$ 273.0670, found 273.0675.

*Methyl 2-(2-Methoxyphenyl)-4λ⁴-[1,3,4]oxadiazolo[3,2-a]pyridine-6-carboxylate perchlorate (**3e**).* White solid: Yield 1.01 g (79%); mp (DSC) (10 °C/min) onset 238.78 °C, maximum 242.63 °C; IR (ATR) ν_{max} 3078, 1733, 1642, 1608, 1556, 1510, 1495, 1452, 1305, 1287, 1130, 1077, 1053, 1038 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ_H: 4.01 (s, 3H), 4.06 (s, 3H), 7.33, (t, J = 7.6 Hz, 1H), 7.48 (d, J = 8.4 Hz, 1H), 7.88 (t, J = 7.2 Hz, 1H), 8.15 (m, 1H), 8.79 (d, J = 9.2 Hz, 1H), 9.08 (m, 1H), 10.33 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ_C: 54.1, 57.1, 108.4, 111.8, 114.1, 122.0, 126.0, 131.6, 135.6, 138.0, 144.2, 154.6, 159.8, 162.5, 164.6; *m/z* 285.1; HRMS (ESI) calcd for $C_{15}H_{13}N_2O_4$ $[M^+]$ 285.0870, found 285.0873

*Methyl 2-(3-Methoxyphenyl)-4λ⁴-[1,3,4]oxadiazolo[3,2-a]pyridine-6-carboxylate perchlorate (**3f**).* White solid: Yield 1.01 g (79%); mp (DSC) (10 °C/min) onset 211.73 °C, maximum 217.20 °C; IR (ATR) ν_{max} 3103, 1744, 1641, 1617, 1568, 1483, 1461, 1440, 1299, 1289, 1260, 1087, 1027 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ_H: 3.92 (s, 3H), 4.01, (s, 3H), 7.50, (dd, J = 8.4 Hz, 2.0 Hz, 1H), 7.70 (t, J = 2.4 Hz, 1H), 7.74 (t, J = 8.0 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 8.80 (d, J = 9.2 Hz, 1H), 9.12 (dd, J = 9.2 Hz, 1.2 Hz, 1H), 10.33 (1H, d, J = 1.2 Hz); ^{13}C NMR (100 MHz, DMSO) δ_C: 54.2, 56.3, 109.1, 112.1, 113.1, 121.2, 122.4, 126.3, 132.3, 135.7, 144.8, 155.2, 160.5, 162.4, 165.8; *m/z* 285.1; HRMS (ESI) calcd for $C_{15}H_{13}N_2O_4$ $[M^+]$ 285.0870, found 285.0874

*Methyl 2-(4-Methoxyphenyl)-4λ⁴-[1,3,4]oxadiazolo[3,2-a]pyridine-6-carboxylate perchlorate (**3g**).* White solid: Yield 1.1 g (70%); mp (DSC) (10 °C/min) onset 244.17 °C, maximum 245.03 °C; IR (ATR) ν_{max} 3102, 1738, 1645, 1601, 1505, 1322, 1294, 1271, 1093, 1009 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ_H: 3.94 (s, 3H), 4.00 (s, 3H), 7.33 (d, J = 9.0 Hz, 2H), 8.23 (d, J = 9.2 Hz, 2H), 8.76 (d, J = 9.2 Hz, 1H), 9.06 (d, J = 9.2 Hz, 1H), 10.27 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ_C: 54.1, 56.5, 111.8, 116.4, 126.0, 131.2, 135.4, 139.4, 144.1, 155.1, 162.5, 165.5, 165.9; *m/z* 285.1; HRMS (ESI) calcd for $C_{15}H_{13}N_2O_4$ $[M^+]$ 285.0870, found 285.0873

*Methyl 2-(m-Tolyl)-4λ⁴-[1,3,4]oxadiazolo[3,2-a]pyridine-6-carboxylate perchlorate (**3i**).* White solid: Yield 0.83 g (64%); mp (DSC) (10 °C/min) onset 220.15 °C, maximum 221.48 °C; IR (ATR) ν_{max} 3090, 1746, 1645, 1611, 1565, 1611, 1565, 1480, 1431, 1302, 1197, 1088 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ_H: 2.49 (s, 3H), 4.01 (s, 3H), 7.71 (m, 2H), 8.09 (m, 2H), 8.81 (d, J = 9.6 Hz, 1H), 9.11 (dd, J = 1.1, 9.2 Hz, 1H), 10.33 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ_C: 21.2, 54.2, 112.0, 120.1, 126.2, 126.2, 128.9, 130.7, 135.7, 137.0, 140.6, 144.6, 155.2, 162.4, 166.0; *m/z* 269.1; HRMS (ESI) calcd for $C_{15}H_{13}N_2O_3$ $[M^+]$ 269.0921, found 269.0924

*Methyl 2-(p-Tolyl)-4λ⁴-[1,3,4]oxadiazolo[3,2-a]pyridine-6-carboxylate perchlorate (**3j**).* White solid: Yield 0.80 g (80%); mp (DSC) (10 °C/min) onset 233.77 °C, maximum 235.82 °C; IR (ATR) ν_{max} 3095, 1730, 1644, 1613, 1563, 1505, 1434, 1304, 1290, 1188, 1092 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ_H: 2.49 (s, 3H), 4.01 (s, 3H), 7.61 (d, J = 8 Hz, 2H), 8.09 (d, J = 8 Hz, 2H), 8.78 (d, J = 9.2 Hz, 1H), 9.09 (dd, J = 8 Hz, 1.2 Hz, 1H), 10.30 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ_C: 22.0, 54.2, 111.9, 117.2, 126.1, 128.9, 131.4, 135.6, 144.4, 147.4, 155.1, 162.5, 166.2; *m/z* 269.1; HRMS (ESI) calcd for $C_{15}H_{13}N_2O_3$ $[M^+]$ 269.0921, found 269.0924

*Methyl 2-(Rhiophen-2-yl)-4λ⁴-[1,3,4]oxadiazolo[3,2-a]pyridine-6-carboxylate perchlorate (**3l**).* White solid: Yield 0.53 g (82%); mp (DSC) (10 °C/min) onset 200.90 °C, maximum 204.20 °C; IR (ATR) ν_{max} 3093, 1727, 1644, 1608, 1580, 1439, 1320, 1300, 1133, 1092, 1078, 1065 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ_H: 3.99 (s, 3H), 7.52, (t, J = 8 Hz, 1H), 8.37 (d, J = 3.6 Hz, 1H,), 8.40 (d, J = 4.8 Hz, 1H), 8.78 (d, J = 9.2 Hz, 1H), 9.09 (dd, J = 9.2, 1.2 Hz, 1H), 10.29 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ_C: 54.2, 111.8, 120.5, 126.2, 130.8, 135.5, 136.9, 138.8, 144.5, 154.8, 162.2, 162.4; *m/z* 261.0; HRMS (ESI) calcd for $C_{12}H_9N_2O_3S$ $[M^+]$ 261.0328, found 261.0333

*Methyl 2-(4-Methylbenzyl)-4λ⁴-[1,3,4]oxadiazolo[3,2-a]pyridine-6-carboxylate perchlorate (**3m**).* White solid: Yield 0.35 g (74%); mp (DSC) (10 °C/min) onset 178.78 °C, maximum 180.26 °C; IR (ATR) ν_{max} 3083, 2954, 1743, 1636, 1604, 1598, 1495, 1456, 1402, 1324, 1304, 1169, 1084 cm^{-1}; ^1H NMR (400 MHz, DMSO) 3.98 (s, 3H), 4.75 (s, 2H), 7.33−52 (m, 5H), 8.74 (d, J = 9.2 Hz, 1H), 9.06 (d, J = 9.2 Hz, 1H), 10.25 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ_C: 31.5, 54.1, 112.0, 125.9, 128.5, 129.4, 130.2, 131.9, 135.7, 144.6, 155.3, 162.5, 169.7; *m/z* 269.1; HRMS (ESI) calcd for $C_{15}H_{13}N_2O_3$ $[M^+]$ 269.0921, found 269.0924

*6-(Methoxycarbonyl)-2-methyl-[1,3,4]oxadiazolo[3,2-a]pyridin-4-ium perchlorate (**3n**).* Orange waxy solid: Yield 0.45 g (64%); mp (DSC) (10 °C/min) 104 °C (decomposes); IR (ATR) ν_{max} 3161, 1723, 1647, 1619, 1587, 1439, 1315, 1208, 1084 cm^{-1}; ^1H NMR (400 MHz, DMSO) 2.94 (s, 3H), 3.99 (s, 3H), 8.74 (d, J = 9.2 Hz, 1H), 9.06 (d, J = 9.2 Hz, 1H), 10.21 (s, 1H);^{13}C NMR (100 MHz, DMSO) δ_C: 11.9, 54.1, 111.8, 125.9, 135.5, 144.4, 155.2, 162.5, 168.8; *m/z* 193.1.; HRMS (ESI) calcd for $C_9H_9N_2O_3$ $[M^+]$ 193.0608, found 193.0612

*2-(Tert-butyl)-6-(methoxycarbonyl)-[1,3,4]oxadiazolo[3,2-a]pyridin-4-ium (**3o**).* White solid: Yield 0.39 g (67%); mp (DSC) (10 °C/min) onset 144.76 °C, maximum 148.46 °C; IR (ATR) ν_{max} 3083, 2980, 1729, 1647, 1602, 1515, 1458, 1440, 1366, 1320, 1310, 1206, 1175, 1123, 1087 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ_H: 1.53 (s, 9H), 3.99 (s, 3H), 8.73 (d, J = 9.2 Hz, 1H), 9.06 (d, J = 9.2 Hz, 1H), 10.26 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ_C: 27.4, 33.5, 54.1, 112.1, 125.9, 135.6, 144.4, 155.5, 162.5, 176.1; *m/z* 235.1. HRMS (ESI) calcd for $C_{12}H_{15}N_2O_3$ $[M^+]$ 235.1077, found 235.1080

*Methyl 2-Phenyl-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (**1a**).* White solid: Yield 0.05 g (28%). With 3 eq. acetic anhydride, 130 °C, Yield 0.12 g (84%); mp (DSC) (10 °C/min) onset 149.27 °C, maximum 150.01 °C; IR (ATR) ν_{max} 2953, 1724, 1638, 1450, 1438, 1319, 1334, 1307, 1297, 1201, 1135 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ_H: 3.90 (s, 3H), 7.54 (m, 3H), 7.92 (d, J = 9.2 Hz, 1H), 8.04 (d, J = 9.2 Hz, 1H), 8.21 (m, 2H), 9.46 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ_C: 53.1, 116.1, 117.9, 127.5, 129.5, 130.1, 130.4, 131.1, 132.5, 152.9, 164.6, 165.3; *m/z* 254.1; HRMS (ESI) calcd for $C_{14}H_{12}N_3O_2$ $[M+H^+]$ 254.0924, found 254.0926

*Methyl 2-(2-Fluorophenyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (**1b**).* White solid: Yield 0.28 g (53%); mp (DSC) (10 °C/min) onset 157.72 °C, maximum 158.80 °C; IR (ATR) n_{max} 2955, 1719, 1639, 1617, 1587, 1512, 1474, 1448, 1439, 1321, 1305, 1289, 1197, 1140, 1128 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ_H: 3.91 (s, 3H), 7.39 (q, J = 6.8 Hz, 2H), 7.59 (m, 1H), 7.64 (d, J = 9.6 Hz, 1H), 8.06 (d, J = 9.2 Hz, 1H), 8.19 (t, J = 7.6 Hz, 1H), 9.51 (br s, 1H); ^{19}F δ_F: −111.1; ^{13}C NMR (100 MHz, DMSO) δ_C: 53.2, 116.2, 117.3 (d, J = 19 Hz), 118.1, 118.4 (d, J = 9 Hz) 125.3, 130.2, 131.3 (d, J = 3 Hz), 132.5, 133.0 (d, J = 9.5 Hz), 152.2, 160.5 (d, J = 256 Hz), 162.0, 164.6; *m/z* 272.1; HRMS (ESI) calcd for $C_{14}H_{11}N_3O_2F$ $[M+H^+]$ 272.0830, found 272.0833

*Methyl 2-(3-Fluorophenyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (**1c**).* White solid: Yield 0.29 g (55%); mp (DSC) (10 °C/min) onset 150.20 °C, maximum 154.78 °C; IR (ATR) ν_{max} 2959, 1723, 1638, 1590, 1512, 1434, 1322, 1296, 1217, 1103 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ_H: 3.90 (s, 3H), 7.39 (m, 2H), 7.59

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(m, 1H), 7.95 (d, J = 9.4 Hz, 1H), 8.06 (d, J = 9.4 Hz, 1H), 8.19 (t, J = 7.2 Hz, 1H), 9.51 (s, 1H); ^{19}F δ_F: −112.3; ^{13}C NMR (100 MHz, DMSO) δ_C: 53.2, 113.9 (d, J = 27 Hz), 116.3, 117.9 (d, J = 22 Hz), 118.2, 123.6 (d, J = 3 Hz), 130.3, 131.8 d, J = 9 Hz), 132.5, 132.8, 152.9, 161.6, 164.1, 164.6; *m/z* 272.1; HRMS (ESI) calcd for $C_{14}H_{11}N_3O_2F$ [M+H$^+$] 272.0830, found 272.0832

*Methyl 2-(4-Fluorophenyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (**1d**).* White solid: Yield 0.25 g (43%); mp (DSC) (10 °C/min) onset 152.21 °C, maximum 154.16 °C; IR (ATR) ν_{max} 2959, 1730, 1641, 1609, 1529, 1457, 1440, 1323, 1300, 1261, 1198, 1156, 1139 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ_H: 3.90 (s, 3H), 7.38 (t, J = 8.8 Hz, 2H), 7.91 (d, J = 9.2 Hz, 1H), 8.04 (m, 1H), 8.23 (m, 2H), 9.45 (s, 1H); ^{19}F δ_F: −110.1; ^{13}C NMR (100 MHz, DMSO) δ_C: 53.1, 116.1, 116.5 (d, J = 21 Hz), 118.0, 127.0 (d, J = 3 Hz) 129.8 (d, J = 10 Hz), 130.2, 132.5, 152.9, 164.0 (d, J = 249 Hz), 164.5, 164.6; *m/z* 272.1; HRMS (ESI) calcd for $C_{14}H_{11}N_3O_2F$ [M+H$^+$] 272.0830, found 272.0835

*Methyl 2-(2-Methoxyphenyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (**1e**).* White solid: Yield 0.46 g (52%); mp (DSC) (10 °C/min) onset 105.35 °C, maximum 106.07 °C; IR (ATR) ν_{max} 3061, 2956, 1721, 1636, 1608, 1587, 1512, 1477, 1445, 1434, 1329, 1300, 1286, 1257, 1247, 1127 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ_H: 3.84 (s, 3H), 3.90 (s, 3H), 7.08 (t, J = 7.6 Hz, 1H), 7.20 (d, J = 8.4 Hz, 1H), 7.50 (m, 1H), 7.90 (m, 2H), 8.02 (m, 1H), 9.45 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ_C: 53.1, 56.2, 110.0, 112.8, 115.9, 117.6, 120.8, 129.7, 131.7, 132.1, 132.3, 151.9, 158.1, 164.4, 164.7; *m/z* 284.1.1; HRMS (ESI) calcd for $C_{15}H_{14}N_3O_3$ [M+H$^+$] 284.1030, found 284.1032

*Methyl 2-(3-Methoxyphenyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (**1f**).* White solid: Yield 0.42 g (66%); mp (DSC) (10 °C/min) onset 130.98 °C, maximum 132.13 °C; IR (ATR) ν_{max} 3079, 2961, 1730, 1640, 1593, 1480, 1433, 1318, 1272, 1239, 1134 cm^{-1}. ^{1}H NMR (400 MHz, DMSO) δ_H: 3.84 (s, 3H), 3.91 (s, 3H), 7.10 (dd, J = 2.4, 8.4 Hz, 1H), 7.46, (t, J = 8 Hz, 1H), 7.72 (s, 1H), 7.79 (d, J = 8 Hz, 1H), 7.93 (d, J = 9.6 Hz, 1H), 8.05 (d, J = 9.6 Hz, 1H) 9.49 (s, 1H). ^{13}C NMR (100 MHz, DMSO) δ_C: 53.2, 55.7, 112.2, 116.1, 117.1, 118.0, 119.8, 130.2, 130.7, 131.7, 132.5, 152.9, 160.0, 164.6, 165.2. *m/z* 284.1.1. HRMS (ESI) calcd for $C_{15}H_{14}N_3O_3$ [M+H$^+$] 284.1030, found 284.1032

*Methyl 2-(4-Methoxyphenyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (**1g**).* White solid: Yield 0.54 g (94%); mp (DSC) (10 °C/min) onset 185.70 °C, maximum 186.30 °C; IR (ATR) ν_{max} 2950, 1711, 1637, 1611, 1532, 1460, 1445, 1427, 1320, 1295, 1248, 1200, 1185, 1167, 1027, 837 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ_H: 3.82 (s, 3H), 3.90 (s, 3H), 7.09 (d, J = 8.8 Hz, 2H), 7.87 (d, J = 9.2 Hz, 1H), 8.02 (d, J = 9.2 Hz, 1H), 8.14 (d, J = 8.8 Hz, 2H), 9.43 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ_C: 53.1, 55.8, 114.9, 115.8, 117.6, 122.8, 129.1, 130.0, 132.3, 152.9, 161.7, 164.7, 165.3; *m/z* 284.1.1; HRMS (ESI) calcd for $C_{15}H_{14}N_3O_3$ [M+H$^+$] 284.1030, found 284.1032

*Methyl 2-(m-Tolyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (**1i**).* Off-white solid: Yield 0.44 g (68%); mp (DSC) (10 °C/min) 142 °C (decomposes); IR (ATR) ν_{max} 3012, 2956, 1721, 1637, 1509, 1439, 1320, 1307, 1296, 1198, 1116, 1037 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$-DMSO) δ_H: 2.45 (s, 3H), 3.99 (s, 3H), 7.20 (m, 1H), 7.65 (d, J = 6.4 Hz, 1H), 7.98 (m, 3H), 9.19 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 21.4, 52.8, 115.5, 117.8, 124.7, 128.1, 128.8, 129.7, 129.8, 131.5, 131.7, 138.6, 152.7, 164.5, 166.0; *m/z* 268.1.1; HRMS (ESI) calcd for $C_{15}H_{14}N_3O_2$ [M+H$^+$] 268.1081, found 268.1085

*Methyl 2-(p-Tolyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (**1j**).* White solid: Yield 0.49 g (82%); mp (DSC) (10 °C/min) 91 °C (decomposes); IR (ATR) ν_{max} 3076, 2953, 1721, 1639, 1614, 1459, 1436, 1346, 1323, 1304, 1197, 1186, 1135, 960 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.42 (s, 3H), 3.98 (s, 3H), 7.30 (d, J = 8.0 Hz, 2H), 7.72 (d, J = 9.2 Hz, 1H), 8.02 (d, J = 9.2 Hz, 1H), 8.16 (d, J = 8.0 Hz, 2H), 9.26 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ_C: 21.5, 52.7, 115.4, 117.5, 127.3, 127.4, 129.45, 129.5, 131.6, 140.9, 152.8, 164.5, 166.2; *m/z* 268.1.1; HRMS (ESI) calcd for $C_{15}H_{14}N_3O_2$ [M+H$^+$] 268.1081, found 268.1085

*Methyl 2-(Thiophen-2-yl)-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (**1l**).* White solid: Yield 0.16 g (30%); mp (DSC) (10 °C/min) onset 174.28 °C, maximum 174.87 °C; IR (ATR) ν_{max} 3082, 2951, 1710, 1639, 1566, 1509, 1473, 1441, 1393, 1356, 1324, 1308, 1291, 1224, 1204, 1140, 1106 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.90 (s, 3H), 7.23 (m, 1H), 7.78, (d, J = 6.7 Hz, 1H), 7.86 (m, 2H), 8.03 (dd, J = 9, 12 Hz, 1H), 9.43 (s, 1H); ^{13}C NMR (100 MHz, DMSO). δ_C: 53.1, 115.8, 117.9, 128.9, 130.1, 130.4, 132.3, 133.0, 139.6, 152.7, 161.4, 164.6; *m/z* 260.0.1; HRMS (ESI) calcd for $C_{12}H_{10}N_3O_2S$ [M+H$^+$] 260.0488, found 260.0491

*Methyl 2-Benzyl-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (**1m**).* White solid. With 3 eq. acetic anhydride, 130 °C. Isolated by trituration with MTBE: Yield 0.14 g (72%); mp (DSC) (10 °C/min) onset 107.54 °C, maximum 108.90 °C; IR (ATR) ν_{max} 3065, 3032, 2956, 1723, 1638, 1518, 1453, 1439, 1337, 1319, 1293, 1205, 1155, 1135, 1020 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.98 (s, 3H), 4.30 (s, 2H), 7.25 (m, 1H), 7.33 (t, J = 7.6 Hz, 2H), 7.41 (d, J = 7.2 Hz, 2H), 7.71 (d, J = 8.2 Hz, 1H), 8.07 (dd, J = 9.8, 1.2 Hz, 1H), 9.22 (s, 1H).;^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 35.2, 52.8, 115.3, 117.8, 126.9, 128.7, 129.0, 129.8, 131.6, 136.9, 152.1, 164.4, 167.9; *m/z* 268.1; HRMS (ESI) calcd for $C_{15}H_{14}N_3O_2$ [M+H$^+$] 268.1081, found 268.1085

*Methyl 2-Methyl-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (**1n**).* Not isolated: *m/z* 192.1

*Methyl 2-(tert-Butyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (**1o**).* Not isolated: *m/z* 234.1; HRMS (ESI) calcd for $C_{12}H_{16}N_3O_2$ [M+H$^+$] 234.1237, found 234.1241

*Methyl 1-Benzimidamido-6-oxo-1,6-dihydropyridine-3-carboxylate (**6a**).* Pale yellow solid: Yield 1.21 g (80%); mp (DSC) (10 °C/min) 183 °C (decomposes); IR (ATR) ν_{max} 3425, 3338, 3231, 1720, 1647, 1586, 1550, 1442, 1416, 1272, 1106 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ_H: 3.76 (s, 3H), 6.47 (d, J = 9.2 Hz, 1H), 7.15 (brs, 2H), 7.47 (m, 2H), 7.54 (m, 1H), 7.73 (dd, J = 2.4, 9.2 Hz), 1H), 7.88 (d, J = 9.2 Hz, 1H), 8.10 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO) δ_C: 52.2, 108.5, 119.9, 127.8, 128.6, 131.4, 133.3, 136.8, 142.6, 158.9, 162.1, 164.8; *m/z* 272.1; HRMS (ESI) calcd for $C_{14}H_{14}N_3O_3$ [M+H$^+$] 272.1030, found 272.1036

*Methyl (Z)-1-((Amino(4-fluorophenyl)methylene)amino)-6-oxo-1,6-dihydropyridine-3-carboxylate (**6d**).* Yellow solid. Isolated by filtration: Yield 3.67 g (77%); mp (DSC) (10 °C/min) onset 281.76 °C, maximum 283.15 °C; IR (ATR) ν_{max} 3420, 3335, 3225, 1722, 1644, 1606, 1587, 1558, 1535, 1443, 1418, 1308, 1273, 1106 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ_H: 3.75 (s, 3H), 6.47 (d, J = 9.6 Hz, 1H), 7.18 (brs, 2H), 7.31 (t, J = 8.8 Hz, 2H), 7.73 (d, 9.6 Hz, 1H), 7.95 (m, 2H), 8.12 (s, 1H); ^{19}F δ_F: −109.8; ^{13}C NMR (100 MHz, DMSO) δ_C: 53.2, 108.5, 115.20, 119.9, 129.7, 130.3, 136.8, 142.6, 158.9, 161.1, 164.2, 164.8; *m/z* 290.1; HRMS (ESI) calcd for $C_{14}H_{13}N_3O_3F$ [M+H$^+$] 290.0935, found 290.0940.

*Methyl (Z)-1-((Amino(pyridin-2-yl)methylene)amino)-6-oxo-1,6-dihydropyridine-3-carboxylate (**6k**).* Yellow solid. Isolated by filtration, no workup: Yield 12.0 g (90%); mp (DSC) (10 °C/min) onset 237.30 °C, maximum 238.96 °C; IR (ATR) ν_{max} 3388, 3314, 3260, 1720, 1676, 1643, 1595, 1561, 1443, 1407, 1313, 1298, 1276, 1262, 1117 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ_H: 3.86 (s, 3H), 6.65 (d, J = 9.6 Hz, 1H), 7.45 (m, 1H), 7.88 (m, 2H), 8.32 (m, 2H), 8.59 (d, J = 3.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO) δ_C: 52.1, 109.8, 119.8, 122.1, 126.1, 137.0, 137.5, 146.7,141.9, 148.2, 148.24, 158.0, 159.1, 164.6; *m/z* 273.1; HRMS (ESI) calcd for $C_{13}H_{13}N_4O_3$ [M+H$^+$] 273.0982, found 273.0988.

*(Z)-1-((Amino(phenyl)methylene)amino)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (**9a**).* Pale yellow solid: Yield 0.16 g (50%); mp (DSC) (10 °C/min) onset 263.15 °C, maximum 265.27 °C; IR (ATR) νmax 3445, 3311, 3213, 1700, 1634, 1600, 1557, 1535, 1437, 1400, 1242, 1216, 1132 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ_H: 6.45 (d, J = 9.2 Hz, 1H), 7.12 (brs, 2H), 7.46 (m, 2H), 7.53 (m, 1H), 7.72 (dd, J = 2.4, 9.2 Hz), 1H), 7.88 (d, J = 9.2 Hz, 1H), 8.04 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO) δ_C: 109.5, 119.8, 127.8, 128.6, 131.4, 133.3, 137.2, 142.4, 159.0, 162.0, 165.8; *m/z* 258.1; HRMS (ESI) calcd for $C_{13}H_{12}N_3O_3$ [M+H+] 258.0873, found 258.0882

*(Z)-1-((Amino(4-fluorophenyl)methylene)amino)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (**9d**).* White solid. Isolated by filtration: Yield 3.67 g (77%); mp (DSC) (10 °C/min) onset 281.76 °C, maximum 283.15 °C; IR (ATR) ν_{max} 3431, 3330, 3230, 1699, 1646, 1608,

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J. Org. Chem. 2017, 82, 6279−6288

1562, 1532, 1518, 1449, 1415, 1320, 1272, 1231, 1164, 1117, 834 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ_H: 3.75 (s, 3H), 6.44 (d, J = 9.6 Hz, 1H), 7.20 (brs, 1H), 7.31 (t, J = 8.8 Hz, 2H), 7.73 (d, 9.6 Hz, 1H), 7.94 (m, 2H), 8.04 (s, 1H); ^{19}F δ_F: −109.8; ^{13}C NMR (100 MHz, DMSO) δ_C: 109.6, 115.6, 119.7, 129.76, 130.3, 137.3, 142.4, 158.9, 161.0, 164.2, 165.9; *m/z* 276.1; HRMS (ESI) calcd for $C_{13}H_{11}N_3O_3F$ $[M+H^+]$ 276.0779, found 276.0784.

*(Z)-1-((Amino(pyridin-2-yl)methylene)amino)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (**9k**).* White solid: Yield 0.90 g (97%); mp (DSC) (10 °C/min) onset 300.22 °C, maximum 300.77 °C; IR (ATR) ν_{max} 3441, 3224, 1714, 1697.5, 1648, 1623, 1586, 1534, 1440, 1397, 1363, 1282, 1239, 1209, 1132, 770, 763 cm^{-1}; ^1H NMR (400 MHz, TFA-d_1) δ_H: 7.21 (d, J = 9.5 Hz, 1H), 8.40 (dd, 1H, J = 8.1, 9.9 Hz), 8.43 (d, J = 9.5 Hz, 1H), 8.68 (d, 1H), 8.76 (d, J = 8.1 Hz, 1H), 8.91 (dd, J = 8.1, 8.1 Hz, 1H), 9.07 (d, J = 9.9 Hz, 1H); ^{13}C NMR (125 MHz, TFA) δ_C: 115.1, 119.1, 125.8, 130.1, 141.1, 141.7, 141.8, 143.1, 148.5, 154.51, 161.7, 167.7; *m/z* 259.1; HRMS (ESI) calcd for $C_{12}H_{11}N_4O_3$ $[M+H^+]$ 259.0831, found 259.0833.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00873.

1-D and 2-D NMR characterization of **E**, ^1H NMR, ^{13}C NMR spectra of all other compounds (PDF)

Crystallographic information (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: Harry.moloney@gmail.com

*E-mail: Moloney_harry@lilly.com

ORCID

Harold Moloney: 0000-0002-0864-7939

Notes

The authors declare no competing financial interest.

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J. Org. Chem. 2017, 82, 6279−6288