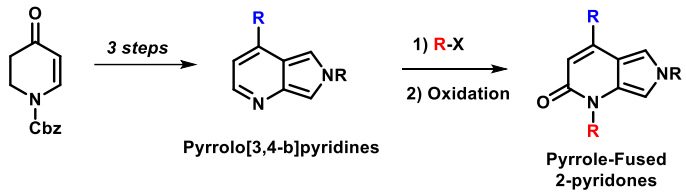
TITLE: A Facile Synthesis of 4-azaisoindoles and their Transformation into Novel Pyrrole-Fused 2-pyridones

Sezgin Kiren*, Felicia Grimes, Hassan Mohammed and Doaa Alazawi

* *Winston Salem State University, 601 MLK, Jr., Winston Salem, NC 27110*

ABSTRACT



We describe herein a novel, efficient and practical synthetic approach to access pyrrolo[3,4-b]pyridines from dihydropyridones in three steps, in which a pyrrole unit is generated from a dihydropyridone using TosMIC reagent. Protection of the resulting pyrrole, Grignard addition followed by oxidative aromatization afford substituted pyrrolo[3,4-b]pyridines. These underutilized structures are subsequently transformed to novel pyrrole-fused 2-pyridones via *N*-alkylation and then oxidation.

1. INTRODUCTION

Pyrrolo[3,4-b]pyridines, also known as azaisoindoles, are 10π heteroaromatic systems hosting fused pyrrole and pyridine rings. As these systems are isosteric to indoles, they have attracted much attention for a broad spectrum of applications in biology, organic chemistry and material sciences.[1] Even though they are reported to be relatively unstable, there are a number of available methodologies, which are mainly developed for the synthesis of an isoindole ring.[1] Among them are 1,3-dipolar cycloaddition of azides onto alkenes,[2] the intramolecular ring closure of benzylic amines by means of a 1,4-addition to α,β-unsaturated esters,[3] condensation of *o*-phthalaldehyde with primary amines,[4] ring closure of nitrones onto alkynes in the presence of a gold catalyst,[5] and 1,3-dipolar cycloaddition of arynes with munchnones.[6] Interestingly, most of the current methodologies focus on the formation of the pyrrole unit from substituted pyridines and, more notably, have drawbacks in terms of step number and overall yields, mainly due to employing highly advanced starting materials. Moreover, these heteroaromatics have solely been employed as a diene partner in Diels-Alder reactions as they possess *o*-quinoid motif in their structure, which is also applied to prove their existence in some methods. Due to inherent instability and limited availability, no other synthetic use has been reported on these heteroaromatics. Therefore, novel, efficient, and practical methods are highly desirable not only to quickly access azaisoindoles from simple and readily available starting materials, but also to study them for further synthetic transformations. Particularly, pyrrole and pyridine rings offer additional functionalization and modification to generate novel and unique heteroaromatic scaffolds, which could find potential applications in various fields.

In continuation of our research program to develop new methods for the synthesis of substituted pyridines by oxidative aromatization,[7] we have become interested in developing a facile and general route to generate azaisoindoles and then investigate their synthetic utility. As indicated in Scheme 1, azaisoindoles (**2**) can be accessed in three steps from the dihydropyridone **1**; a) pyrrole formation using tosylmethyl isocyanide (TosMIC) under basic conditions, b) protection of the resulting pyrrole with a robust

protecting group, c) Grignard addition followed by oxidative aromatization, which is the key step in this protocol. It is expected that the corresponding alcohols without isolation, after a nucleophile addition, could generate **2** in a single operation under acidic, basic, and neutral conditions.

As this protocol allows facile access to azaisoindoles (**2**), their synthetic exploitation will also be possible to generate novel fused heterocycles. As such, the pyridine ring in these compounds can readily be *N*-alkylated using alky halides to form quinolinium-type salts.[8] Subsequently, the oxidation of these salts can result in the formation of structurally novel and intriguing scaffolds, pyrrolo[3.4-b]pyridine-2-ones (**3**), containing pyrrole and 2-pyridone rings. Especially, 2-pyridones are significant class of heteroaromatic scaffolds and building blocks that are observed within natural products, pharmaceuticals, agrochemicals and materials.[9] Additionally, **3** resembles another privileged motif 2-quinolones, benzene-fused 2-pyridones,[10] as the benzene ring is replaced by a pyrrole ring. Similarly, 2-quinolones are prominent heterocyclic core located in compounds that exhibit remarkable pharmacological properties such as anticancer, antibacterial, antifungal, anti-inflammatory, antiviral, antitumor and other activities (Figure 1). As functionalization and decoration of 2-pyridone and 2-quinolone ring systems play a key strategy in generating molecules with improved biological profile and material-related properties, these unique frameworks (**3**) are expected to display promising applications in synthetic and medicinal chemistry.

Scheme 1. Synthesis of 4-substituted Azaisoindoles and their conversion to 2-Quinolone Derivatives

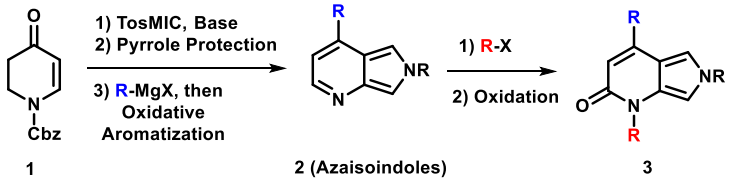
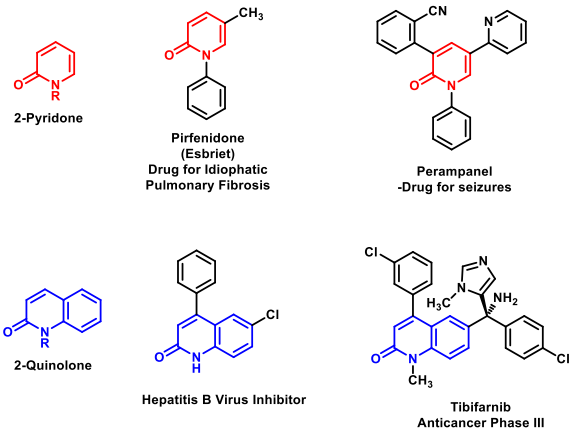


Figure 1. Selected examples bearing 2-pyridone and 2-quinolone skeletons

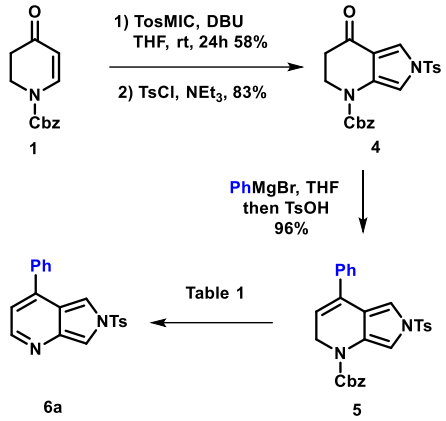


2. RESULTS and DISCUSSIONS

According to literature reports, toluenesulfonylmethyl isocyanide (TosMIC) has proven to be a versatile reagent for providing ready access to substituted pyrroles from electron-deficient olefins under basic conditions.[11] Thus, the pyrrole formation with **1** using TosMIC reagent under basic condition was realized in 58% yield. As pyrroles are prone to polymerization and oxidation, tosyl chloride, as a robust

electron withdrawing group, was chosen for the protection with the intention of enhancing the stability of the final product azaisoindoles. Moreover, this group can prevent side reactions that can take place due to high level reactivity of the pyrrole unit in **2** as a diene in cycloaddition reactions. After facile tosylation of the pyrrole product in 83% yield, phenylmagnesium bromide was added to furnish a mixture of the corresponding alcohol and alkene **5**, which was observed by TLC. The crude mixture of this reaction was treated with *p*-toluenesulfonic acid in acetonitrile to force the formation of **5**, which was obtained in 96% yield (see Scheme 2). The oxidative aromatization of **5** was investigated using various conditions as shown in Table 1 to find optimal yield for the formation of **6a**.

Scheme 2. Azaisoindole Synthesis



Oxidative aromatization conditions were screened using neutral, acidic and basic reagents and solvents.[7] Basic conditions such as sodium methoxide in refluxing methanol (entry 1) gave no product and potassium tertiary butoxide in DMSO (entry 2) yielded **6a** in trace amount**.** These reagents led to decomposition of **6a**, probably due to the cleavage of the tosyl group. Neutral reagents, selenium dioxide (entry 3) in refluxing dioxane, also, did not form the product, but, sulfur (entry 4) furnished **6a** in 10% yield. It looked like acidic conditions (entry 5, 6 and 7) worked better and gave the desired product in higher yields. Among the reagents employed in refluxing acetic acid, cerium (IV) sulfate tetrahydrate provided the highest yield, 56%.[12] We also investigated Lewis acids $TiCl_4$ (entry 8) and $AlCl_3$ (entry 9) and obtained **6a** in 5 and 38% yields, respectively.

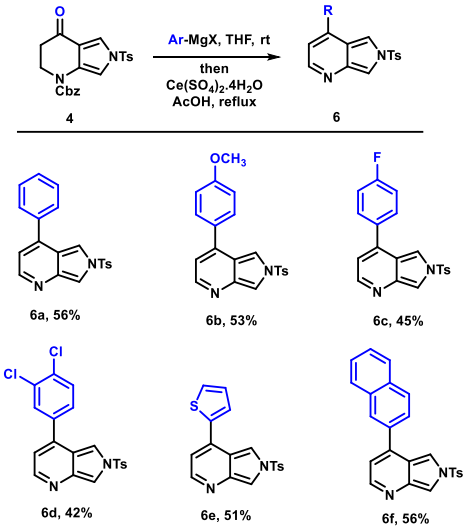
Table 1. Studies for Azaisoindole (**6a**) formation[a,b]

Entry	Reagent (equiv.)	Solvent	Temp (° C)	Time (h)	Yield (%)
1	CH_3ONa (1.2)	CH_3OH	65	16	0
2	t-BuOK (1.2)	DMSO	25	16	<5
3	SeO_2 (1.2)	Dioxane	101	16	0
4	Sulfur (2.0)	Toluene	110	48	10
5	Chloranil (2.0)	AcOH	118	16	26
6	$Cu(OTf)_2$ (2.0)	AcOH	118	16	30
7	**$Ce(SO_4)_2.4H_2O$ (2.0)**	**AcOH**	**100**	**16**	**56**
8	$TiCl_4$ (2.0)	CH_2Cl_2	25	16	5
9	$AlCl_3$ (2.0)	CH_2Cl_2	25	3	38

[a] Yields were determined after purification on silica gel chromatography. [b] All reactions were run open to air.

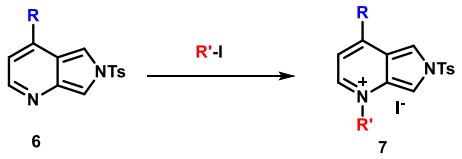
To further demonstrate the efficiency and applicability of this protocol, we turned our attention toward the synthesis of azaisoindoles with various groups at the C-4 position on the pyridine unit, as indicated in Scheme 3. After treatment of **4** with aryl and heteroaryl Grignard reagents, the corresponding alcohols were obtained, which were employed without purification for our optimal oxidative conditions. 4-methoxyphenyl (**6b**), 4-fluorophenyl (**6c**) and 3,4-dicholorophenyl (**6d**) groups were introduced efficiently in two steps in yields of 53%, 45%, and 42% respectively. Additionally, 2-thiphenyl (**6e**) and naphthyl (**6f**) groups were introduced in 51% and 56% yield, respectively. Interestingly, alkyl and allyl Grignard reagents afforded the desired products in low (less than 5%) or no yields under this condition. Nevertheless, as seen from the results, the generation of 4-aryl- or heteroaryl-substituted azaisoindoles can be smoothly realized in an efficient manner with this protocol. It should also be noted that, dehydration of alcohol, Cbz group cleavage and oxidation took place in one pot with a single operation after the addition of a nucleophilic reagent to **4**, which furnished the desired azaisoindole unit (**6**).

Scheme 3. Synthesis of 4-susbtituted Azaisoindoles



After obtaining the azaisoindoles **6a-6f**, they were readily *N*-alkylated on the pyridine nitrogen to form the salts (**7**) as indicated in Table 2. Methyl (**7a**), benzyl salt (**7b**) and methylene ester (**7c**) salts from **6a** are generated using the corresponding iodides at room temperature. The other azaisoindoles **6b-6f** with aryl and heteroaryl substituents were smoothly methylated in moderate to high yields to produce the salts **7d-7h**. In these studies, the azaisoindoles (**6a-6f)** were isolated and purified with column chromatography, which indicated that they did not decompose under the reaction conditions and during work-up. However, they seem to slightly decompose in solution, as observed in NMR solvent. Apparently, in the case of the salts **7a-7h**, the stability is further increased as the reactivity of the pyrrole is diminished by both the tosyl group and the quaternary nitrogen, which is also demonstrated by the earlier reports indicating that electron withdrawing groups on the pyrrole unit increase the stability of azaisoindoles.[1] Notably, these novel salts are structurally derivatives of quinolinium salts (i.e. benzene-fused pyridinium salts), which have been found to possess a variety of applications in biology and material science.[8]

Table 2. Salt Formation from Azaisoindoles[a]

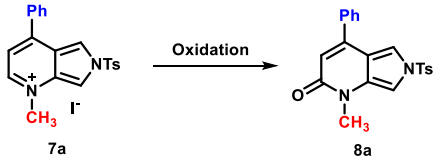


Salts	R	R'	Yield[b] (%)
7a	Phenyl	CH_3	88
7b	Phenyl	Bn	86
7c	Phenyl	CH_2CO_2Et	92
7d	4-Methoxyphenyl	CH_3	87
7e	4-Fluorophenyl	CH_3	76
7f	3,4-Dichlorophenyl	CH_3	75
7g	2-Thiophenyl	CH_3	77
7h	2-Naphthyl	CH_3	72

[a] Reaction conditions: All iodide salts were formed from the corresponding halides at rt for 24h. [b] Isolated yields.

In the literature, there are methods available to oxidize pyridinium and quinolinium salts to generate 2-pyridones and 2-quinolones, respectively. As indicated in Table 3, many of these conditions were investigated to obtain pyrrole-fused 2-pyridones (**8**) by using **7a** as a model substrate. Unfortunately, several oxidizing conditions (entry 1-4) did not result in the formation of **8a**.[13] Base-mediated aerobic oxidation using dimethyl phosphite gave **8a**, but in poor yield (5%, entry 5).[14] In entry 6, *t*-BuOK-promoted aerobic oxidation of **7a** generated **8a** in 13% yield.[15] The yield for **8a** (20%, entry 7) is slightly improved when the same condition was applied under ultrasonic irradiation.[16] Interestingly, **5** is obtained as a side product, probably via intramolecular hydride shift from the adduct that are formed from the addition of *t*-butoxide to the salt. Using potassium ferricyanide under basic conditions as the oxidant, which is the most traditional condition to oxidize pyridinium and quinolinium salts, resulted in the product formation in 22% yield (entry 8).[17] The low yield can be attributed to the base, which could lead to the removal of the tosyl group on the pyrrole. Aerobic oxidation of **7a** using N-heterocyclic carbene under basic condition produced **8a** in 20% yield (entry 9).[18] Pleasingly, the highest yield (36%) for **8a** is obtained when potassium permanganate is used as an oxidant (entry 10).[19]

Table 3. Studies for the oxidation of the salts



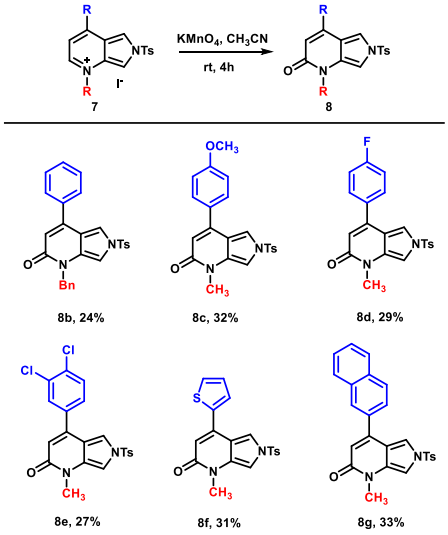
Entry	Conditions[a]	Temp (° C)	Time (h)	Yield[b] (%)
1	H_2O_2, K_2CO_3, CH_3CN	rt	48	0
2	Oxone, $NaHCO_3$, H_2O, CH_3CN	rt	24	0
3	$K_2Cr_2O_7$, H_2O, CH_3CN	rt	24	0
4	m-CPBA, $NaHCO_3$, $CHCl_3$	rt	24	0
5	O_2 (1 atm), $(CH_3O)_2P(O)H$, CH_3CN	40	48	5
6	KO*t*-Bu, air, DMSO	rt	48	13
7	KO*t*-Bu, *t*-BuOH, sonication	rt	0.5	20

8	$K_3[Fe(CN)_6]$, KOH, H_2O	rt	24	22
9	O_2 (1 atm), NHC[c], K_2CO_3, THF	rt	24	20
10	**$KMnO_4$, CH_3CN**	**rt**	**4**	**36**

[a] All reactions were run under air. [b] Yields are obtained after purification on column chromatography. [c]N-heterocyclic carbene (NHC) from 2-Mesityl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate was applied.

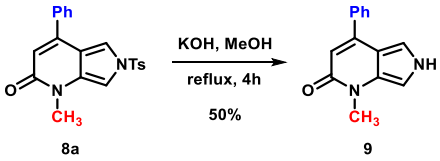
With the optimal condition in hand, the oxidation of the obtained salts with various aryl and heteroaryl groups in the pyridine unit were accomplished as seen in Scheme 4. The benzyl salt **7b** was oxidized to **8b** in 24% yield. The yields for the methyl salts (**7d-7h**) are in low to moderate, and independent of the substituents at the pyridine unit. Similarly, these products seem to be stable under reaction and purification conditions, probably due to extended conjugation of the resulting carbonyl group. Remarkably, these pyrrole-fused 2-pyridones products (**8a-8g**) are structurally unique and intriguing molecules that could have potential applications in various fields.

Scheme 4. Pyrrole Fused-2-pyridones



Lastly, the cleavage of the tosyl group was accomplished by the treatment of **8a** with potassium hydroxide in refluxing methanol, which afforded **9** in the yield of 50 % as shown in Scheme 5. The unprotected pyrrole **9** seems to be stable and can theoretically be protected with various electron withdrawing groups.

Scheme 5. Cleavage of the Tosyl group.



3. CONCLUSIONS

In summary, we have developed a novel and expeditious protocol for the synthesis of 4-aryl or heteroaryl substituted azaisoindoles from readily available starting materials. These underutilized heteroaromatics are then alkylated using various alkyl halides to generate unique pyrrole-fused pyridinium salts. Moreover, these salts were oxidized to pyrrole-fused 2-pyridones in low to moderate yields. It is

anticipated this protocol will be useful for the analogue synthesis of quinolinium salts and 2-quinolone in diverse research areas. Further expansion of the reaction scope and synthetic applications of this methodology are currently under investigation in our laboratory.

4. EXPERIMENTAL SECTION

General Experimental Information

All chemicals were obtained from commercial sources and used directly without further purification. Solvents used in the experiment have been purified over molecular sieve. Reactions were monitored by TLC analysis (pre-coated silica gel 60 F254 plates, 250 μm layer thickness) and visualization was accomplished with a 254 nm UV light. Flash chromatography was performed using SiO_2 to purify the crude reaction mixtures. ^1H and ^{13}C NMR were recorded in 400 MHz apparatus using $CDCl_3$ and acetonitrile-d3 as solvent. The frequency used for measuring ^1H NMR was 400 MHz and 100 MHz for ^{13}C NMR, respectively. Chemical shifts were recorded in ppm by employing TMS as internal standard. HRMS data were obtained under ESI model.

Benzyl 4-oxo-2,3,4,6-tetrahydro-1H-pyrrolo[3,4-b]pyridine-1-carboxylate. To a stirred solution of benzyl 4-oxo-3,4-dihydropyridine-1(2H)-carboxylate (5.0 g, 21.62mmol) in THF (0.2 M) was added TosMIC (8.443 g, 43.24 mmol) and DBU (6.52 mL, 43.24 mmol) at room temperature. The reaction mixture was stirred overnight (24 h) then quenched with saturated NH_4Cl solution. The mixture was extracted with ethyl acetate (3x) and the combined organic extracts were dried over $NaSO_4$. After evaporation of solvent, the crude product was purified by silica gel chromatography (Hexane/EtOAc, 2:1 to 1:1 as eluent) to afford the corresponding pyrrole product (3.4 g, 58% yield) as slightly yellowish white solid. Melting point: 190-192 ºC. IR (ν_{max}/cm^{-1}) 3127.2, 3045.7, 2938.9, 2901.3, 1701.2, 1638.9, 1623.7, 1581.3, 1523.2. ^1H NMR (400 MHz, Chloroform-*d*) 9.32 (brs, 1H), 7.43-7.30 (m, 5H), 7.28 (s,1H), 7.18 (1H, brs), 5.28 (s, 2H), 4.14-4.11 (m, 2H), 2.64 (t, J = 6.4 Hz, 2H). ^{13}C NMR (100 MHz, Chloroform-*d*) 191.20, 153.16, 135.94, 128.70, 128.44, 128.20, 128.14, 118.44, 114.29, 107.66, 67.81, 44.32, 38.13. HRMS (ESI) m/z calculated for $C_{15}H_{15}N_2O_3$ $(M+H)^+$: 271.1083, found: 271.1084.

*Benzyl 4-oxo-6-tosyl-2,3,4,6-tetrahydro-1H-pyrrolo[3,4-b]pyridine-1-carboxylate (**4**).* To a stirred solution of pyrrole (3 g, 11.10 mmol) in 100 ml of acetonitrile (0.1 M) was added triethylamine (1,70 ml, 12.21 mmol) and tosyl chloride (2.24g, 11.65 mmol) at room temperature. The reaction mixture was stirred overnight (24 h) then quenched with saturated NH_4Cl solution. The mixture was extracted with ethyl acetate (3x) and the combined organic extracts were dried over $NaSO_4$. After evaporation of solvent, the crude product was purified by silica gel chromatography (Hexane/EtOAc, 4:1 to 2:1 as eluent) to afford the corresponding product **4** (3.9 g, 83% yield) as white solid. Melting point: 202-204 ºC. IR (ν_{max}/cm^{-1}) 3144.8, 3063.5, 2966.5, 2925.9, 1707.6, 1686.9, 1588.0, 1512.2. ^1H NMR (400 MHz, Chloroform-*d*) 7.79-7.13 (m, 11H), 5.17 (s, 2H), 3.98 (t, J = 6.24 Hz, 2H), 2.53 (t, J = 6.24 Hz, 2H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) 190.37, 152.70, 146.05, 135.54, 134.75, 130.30, 129.72, 128.74, 128.61, 128.35, 128.30, 127.47, 119.96,117.53, 108.80, 68.10, 45.72, 38.28, 21.77. HRMS (ESI) m/z calculated for $C_{22}H_{21}N_2O_5S$ $(M+H)^+$: 425.1171, found: 425.1176.

*Benzyl 4-phenyl-6-tosyl-2,6-dihydro-1H-pyrrolo[3,4-b]pyridine-1-carboxylate (**5**).* To a stirred solution of **4** (1 g, 2.36 mmol) in 30 ml of THF (0.1 M) was added phenyl magnesium bromide (5.34 ml, 0.9 M, 4.72 mmol) and at room temperature. The reaction mixture was stirred 3h then quenched with saturated NH_4Cl solution. The mixture was extracted with ethyl acetate (3x) and the combined organic extracts were dried over $NaSO_4$. After evaporation of the solvent, the crude was dissolved in acetonitrile (10 ml) and then treated with catalytic amount tosyl acid. After stirring a couple of hours, the reaction mixture was quenched with saturated sodium carbonate and extracted with ethyl acetate (3x) and the combined organic extracts were dried over $NaSO_4$. After evaporation of solvent, the crude product was purified by silica gel chromatography (Hexane/EtOAc, 2:1 as eluent) to afford **5** (1.09 g, 96% yield) as brownish white solid. Melting point: 173-175 ^oC. IR (ν_{max}/cm^{-1}) 3064.0, 2922.7, 2897.5, 1704.9, 1651.6, 1595.1. ^1H NMR (400 MHz, Chloroform-*d*) 7.69-7.22 (m, 15H), 6.83 (brs, 1H), 5.62-5.51 (m, 1H), 5.24-5.14 (m, 2H), 4.46 (brs, 2H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) 152.90, 144.80, 138.01, 136.05, 135.77, 131.43, 129.96, 128.71, 128.66, 128.36, 128.16, 128.08, 127.24, 126.99, 126.43, 119.25, 117.78, 114.93, 109.24, 67.69, 45.94, 21.57. HRMS (ESI) m/z calculated for $C_{28}H_{25}N_2O_4S$ $(M+H)^+$: 485.1535, found: 485.1539.

General procedure for Grignard addition and Aromatization. To a stirred solution of tosyl-protected pyrrole compounds (1.0 equiv.) in THF (0.2 M) was added Grignard reagents (2.0 equiv.) at room temperature. The reaction mixture was stirred for a couple of hours, which was determined by TLC, and quenched with saturated NH_4Cl solution. The mixture was extracted with ethyl acetate (3x) and the combined organic extracts were dried over Na_2SO_4. After evaporation of solvent, the crude product was refluxed with cerium (IV) sulfate tetrahydrate (2.0 equiv.) in AcOH (0.05 M) for overnight. The reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with ethyl acetate. The combined extracts are dried over Na_2SO_4 and the solvent is removed under vacuum. The residue is purified with flash chromatography on silica gel using a mixture of hexane and ethyl acetate as an eluent to give the azaisoindole products.

*4-phenyl-6-tosyl-6H-pyrrolo[3,4-b]pyridine (**6a**).* Yellowish foamy solid, 56% yield. Melting point: 123-124 ^oC. IR (KBr disk, ν_{max}/cm^{-1}) 3061.7, 2925.2, 1742.8, 1596.4, 1557.1. ^1H NMR (400 MHz, Chloroform-*d*) 8.42, (d, J=4.2 Hz, 1H), 7.84 (J=2.48 Hz, d, 1H), 7.78 (d, J=8.40 Hz, 2H), 7.63 (d, J=2.44 Hz, 1H), 7.60 (d, J= 8.20 Hz, 2H), 7.44 (m, 3H), 7.23 (d, J=8.60 Hz, 2H), 6.85 (d, J=4.20 Hz, 1H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) 151.26, 146.11, 143.31, 140.53, 137.53, 135.04, 130.28, 129.66, 129.13, 127.90, 127.55, 118.74, 117.13, 111.71, 109.84, 21.68. HRMS (ESI) m/z calculated for $C_{20}H_{17}N_2O_2S$ $(M+H)^+$: 349.1011, found: 349.1014.

*4-(4-methoxyphenyl)-6-tosyl-6H-pyrrolo[3,4-b]pyridine (**6b**).* Yellowish foamy solid, 53% yield; Melting point: 125-126 ^oC. IR (KBr disk, ν_{max}/cm^{-1}) 3062.5, 2925.8, 1733.9, 1593.2, 1557.8. ^1H NMR (400 MHz, Chloroform-*d*) 8.39 (d, J=4.24 Hz, 1H), 7.82 (d, J=2.48 Hz, 1 H), 7.77 (d, J=8.44 Hz, 2H), 7.63 (d, J=2.48 Hz, 1 H), 7.56 (d, J=8.84 Hz, 2H), 7.21 (d, J=8.60 Hz, 2H), 6.97 (d, J=8.84 Hz, 2H), 6.80 (d, J=4.20 Hz, 1H), 3.82 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) 160.61, 151.46, 146.03, 142.63, 140.93, 135.13, 130.24, 129.94, 127.49, 126.99, 118.88, 116.51, 114.00, 111.69, 109.79, 55.45, 21.67. HRMS (ESI) m/z calculated for $C_{21}H_{19}N_2O_3S$ $(M+H)^+$: 379.1116, found: 379.1106.

*4-(4-fluorophenyl)-6-tosyl-6H-pyrrolo[3,4-b]pyridine (**6c**).* Brownish foamy solid, 45% yield. Melting point: 120-121 ^oC. IR (KBr disk, ν_{max}/cm^{-1}) 3063.1, 2924.7, 1732.6, 1603.8, 1531.1. ^1H NMR (400 MHz, Chloroform-*d*) 8.41 (d, J=4.16 Hz, 1H), 7.84 (d, J=2.44 Hz, 1H), 7.78 (dd, J-6.72, 1.72, 2H), 7.60-7.56 (m,

3H), 7.22 (d, J=8.0 Hz, 2H), 7.14 (t, J=8.64, 2H), 6.80 (d, J=4.16 Hz, 1H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) 164.62, 162.14, 151.35, 146.14, 141.85, 140.88, 135.03, 133.67, 133.63, 130.29, 129.66, 127.53, 118.65, 117.15, 116.29, 116.07, 111.96, 109.48, 21.69. HRMS (ESI) m/z calculated for $C_{20}H_{16}FN_2O_2S$ $(M+H)^+$: 367.0917, found: 367.0905.

*4-(3,4-dichlorophenyl)-6-tosyl-6H-pyrrolo[3,4-b]pyridine (**6d**).* Yellowish foamy solid, 42% yield. Melting point: 146-147 ºC. IR (KBr disk, ν_{max}/cm^{-1}) 3059.9, 2920.4, 1734.05, 1594.1, 1541.5. ^{1}H NMR (400 MHz, Chloroform-*d*) 8.47 (d, J=4.05 Hz, 1H), 7.96 (d, J=1.95 Hz, 1H), 7.81 (d, J=8.38 Hz, 2H), 7.67 (dd, J=15.62, 2.10 Hz, 2H), 7.56 (d, J=8.29 Hz, 1H), 7.47 (dd, J=2.10, 8.30 Hz, 1H), 7.26 (d, J=8.10 Hz, 2H), 6.92 (d, J=4.17 Hz, 1H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) 149.58, 146.69, 143.22, 137.65, 136.85, 134.44, 134.26, 133.70, 131.31, 130.49, 129.69, 127.77, 127.13, 118.23, 116.93, 111.46, 109.96, 22.66. HRMS (ESI) m/z calculated for $C_{20}H_{15}C_{l2}N_2O_2S$ $(M+H)^+$: 417.0231, found: 417.0227.

*4-(thiophen-2-yl)-6-tosyl-6H-pyrrolo[3,4-b]pyridine (**6e**).* Dark brownish foamy solid, 51% yield. Melting point: 119-120 ºC. IR (KBr disk, ν_{max}/cm^{-1}) 3064.0, 2960.7, 1733.0, 1594.4, 1574.6. ^{1}H NMR (400 MHz, Chloroform-*d*) 8.41 (d, J=4.72 Hz, 1H), 7.94 (dd, J=6.88, 2.24 Hz, 2H), 7.82 (d, J=8.44 Hz, 2H), 7.75 (d, J=8.3 Hz, 1H), 7.62 (d, J=3.68 Hz, 1H), 7.50 (d, J=5.08 Hz, 1H), 7.26 (d, J=8.16 Hz, 2H), 7.08 (d, J=4.68 Hz, 1H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) 148.20, 146.83, 143.53, 138.73, 134.30, 130.55, 129.70, 128.81, 127.86, 126.47, 126.08, 117.41, 114.52, 111.25, 110.61, 21.76. HRMS (ESI) m/z calculated for $C_{18}H_{15}N_2O_2S_2$ $(M+H)^+$: 355.0575, found: 355.0566.

*4-(naphthalen-2-yl)-6-tosyl-6H-pyrrolo[3,4-b]pyridine (**6f**).* Yellowish foamy solid, 56% yield. Melting point: 107-108 ºC. IR (KBr disk, ν_{max}/cm^{-1}) 3053.8, 2956.6, 1746.8, 1593.6, 1553.0. ^{1}H NMR (400 MHz, Chloroform-*d*) 8.57 (d, J=4.33 Hz, 1H), 8.20 (d, J=1.14 Hz, 1H), 8.02 (m, 2H), 7.96 (m, 2H), 7.88 (d, J=8.44 Hz, 2H), 7.84 (d, J=2.45 Hz, 1 H), 7.79 (dd, J=8.44, 1.74 Hz, 1H), 7.61 (m, 2H), 7.31 (d, J=8.05 Hz, 2H), 7.10 (d, J=4.32 Hz, 1 H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) 150.49, 146.30, 144.52, 139.27, 134.83, 134.66, 133.74, 133.35, 130.34, 129.04, 128.53, 127.85, 127.62, 127.52, 127.18, 126.91, 125.35, 118.97, 117.23, 111.48, 110.24, 21.70. HRMS (ESI) m/z calculated for $C_{24}H_{19}N_2O_2S$ $(M+H)^+$: 399.1167, found: 399.1158.

General procedure for Salt formation. The azaisoindoles are stirred with methyl iodide in excess amount (10 eq.) at room temperature for 24 h. In case of benzyl iodide and methylene ester iodide, acetonitrile (1M) was used as solvent. The salts were precipitated and washed with diethyl ether and dried under vacuum.

*1-methyl-4-phenyl-6-tosyl-6H-pyrrolo[3,4-b]pyridin-1-ium iodide (**7a**).* Orange solid, 88% yield. Melting point: 149-150. IR (ν_{max}/cm^{-1}) 3041.7, 3016.0, 2972.8, 2915.1, 1577.2, 1538.9. ^{1}H NMR (400 MHz, Acetonitrile-d_3) 8.69 (d, J=8.44 Hz, 1H), 8.40 (d, J=2.48 Hz, 1H), 8.32 (d, J=2.48 Hz, 1H), 8.13 (d, J=6.76 Hz, 2H), 7.91 (dd, J=8.24, 1.36 Hz, 2H), 7.74-7.65 (m, 3H), 7.54 (d, J=5.88 Hz, 1H), 7.50 (d, J=8.64 Hz, 2H), 4.34 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, Acetonitrile-d_3) 155.24, 150.22, 148.84, 134.86, 133.43, 132.68, 131.32, 130.72, 130.28, 129.56, 129.08, 119.90, 116.72, 116.42, 107.86, 44.92, 21.36. HRMS (ESI) m/z calculated for $C_{21}H_{19}IN_2O_2S$ $(M-I)^+$: 363.1162, found: 363.1149.

*1-benzyl-4-phenyl-6-tosyl-6H-pyrrolo[3,4-b]pyridin-1-ium iodide (**7b**).* Orange solid, 86% yield. Melting point: 174-175 ºC. IR (ν_{max}/cm^{-1}) 3076.2, 3019.5, 2989.0, 1633.4, 1573.3. ^{1}H NMR (400 MHz, Acetonitrile-d_3) 8.75 (d, J=6.02 Hz, 1H), 8.32 (d, J=2.43 Hz, 1H), 8.21 (d, J=2.43 Hz, 1H), (d, J=8.52 Hz, 1H), 7.89 (m,

2H), 7.68 (m, 2H), 7.53 (d, J=6.00 Hz, 1H), 7.46 (m, 8H), 5.77 (s, 2H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, Acetonitrile-*d*$_3$) 156.39, 149.26, 149.01, 134.89, 133.43, 132.95, 132.64, 131.38, 130.37, 130.17, 129.98, 129.85, 129.74, 129.29, 128.99, 120.59, 116.95, 116.91, 107.63, 60.86, 21.39. HRMS (ESI) m/z calculated for $C_{27}H_{23}IN_2O_2S$ $(M-I)^+$: 439.1474, found: 439.1471.

*1-(2-ethoxy-2-oxoethyl)-4-phenyl-6-tosyl-6H-pyrrolo[3,4-b]pyridin-1-ium iodide (**7c**)*. Orange solid, 92% yield. Melting point: 115-116 ºC. IR (ν_{max}/cm^{-1}) 3031.6, 2979.7, 1742.0, 1603.4, 1574.9. ^{1}H-NMR (400 MHz, $CDCl_3$) 9.60 (d, J=5.87 Hz, 1H), 8,27 (brs, 1H), 8.01 (m, 1H), 7.69 (m, 2H), 7.58 (m, 3H), 7.45 (d, J=5.88 Hz, 1H), 7.35 (d, J=8.36 Hz, 2H), 6.01 (s, 2H), 4.22 (q, J=7.12 Hz, 2H), 2.23 (s, 3H), 1.24 (t, J=7.12 Hz, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) 165.30, 156.23, 151.21, 148.17, 134.35, 132.60, 131.12, 129.98, 129.71, 128.82, 128.73, 119.86, 116.36, 115.41, 106.88, 63.40, 58.07, 21.90, 14.13. HRMS (ESI) m/z calculated for $C_{24}H_{23}IN_2O_4S$ $(M-I)^+$: 435.1378, found: 435.1371.

*4-(4-methoxyphenyl)-1-methyl-6-tosyl-6H-pyrrolo[3,4-b]pyridin-1-ium iodide (**7d**)*. Orange solid, 87% yield. Melting point: 181-182 ºC. IR (ν_{max}/cm^{-1}) 3023.0, 2921.2, 1631.9, 1598.5, 1575.3. ^{1}H-NMR (400 MHz, $CDCl_3$) 9.55 (d, J=5.64 Hz, 1H), 8.16 (d, J=2.36 Hz, 1H), 8.03 (d, J=2.36 Hz, 1H), 8.00 (d, J=8.48 Hz, 2H), 7.71 (d, J=8.84 Hz, 2H), 7.40 (d, J=5.76 Hz, 2 H), 7.37 (d, J=8.12 Hz, 3 H), 4.50 (s, 3H), 3.86 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) 163.36, 154.34, 149.93, 148.11, 132.74, 131.14, 130.74, 130.26, 128.60, 126.68, 119.27, 115.53, 115.48, 115.45, 106.58, 55.78, 44.97, 21.93. HRMS (ESI) m/z calculated for $C_{22}H_{21}IN_2O_3S$ $(M-I)^+$: 393.1273, found: 393.1265.

*4-(4-fluorophenyl)-1-methyl-6-tosyl-6H-pyrrolo[3,4-b]pyridin-1-ium iodide (**7e**)*. Orange solid, 76% yield. Melting point: 172-173 ºC. IR (ν_{max}/cm^{-1}) 3054.3, 2904.0, 1643.9, 1598.6, 1579.9. ^{1}H-NMR (400 MHz, $CDCl_3$) 9.59 (d, J=5.86 Hz, 1H), 8.37 (m ,1H), 8.05 (d, J=8.46 Hz, 2H), 7.96 (brs, 1H), 7.73 (m, 2H), 7.46 (d, J=5.87 Hz, 1H), 7.37 (d, J=8.23 Hz, 2H), 7.25 (t, J=8.45 Hz, 2H), 4.57 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) 166.36, 163.83, 153.28, 150.09, 148.15, 132.53, 131.15, 131.03, 130.94, 130.03, 128.80, 119.36, 117.40, 117.18, 116.63, 114.89, 107.52, 45.79, 21.92. HRMS (ESI) m/z calculated for $C_{21}H_{18}FIN_2O_2S$ $(M-I)^+$: 381.1073, found: 381.1064.

*4-(3,4-dichlorophenyl)-1-methyl-6-tosyl-6H-pyrrolo[3,4-b]pyridin-1-ium iodide (**7f**)*. Orange solid, 75% yield. Melting point: 165-167 ºC. IR (ν_{max}/cm^{-1}) 3019.4, 2908.0, 1634.8, 1598.5, 1574.7. ^{1}H-NMR (400 MHz, CD_3CN) 8.71 (d, J=5.81 Hz, 1H), 8.32 (s. 2H), 8.07 (d, J=8.52 Hz, 1H), 8.01 (d, J=1.90 Hz, 1H), 7.80 (m, 2H), 7.50 (m, 3H), 4.28 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, CD_3CN) 152.72, 150.36, 149.05, 136.23, 135.17, 133.97, 133.42, 132.36, 131.39, 131.21, 130.68, 129.40, 129.10, 119.78, 117.23, 116.51, 107.98, 44.97, 21.40. HRMS (ESI) m/z calculated for $C_{21}H_{17}Cl_2IN_2O_2S$ $(M-I)^+$: 431.0387, found: 431.0387.

*1-methyl-4-(thiophen-2-yl)-6-tosyl-6H-pyrrolo[3,4-b]pyridin-1-ium iodide (**7g**)*. Orange solid, 77% yield. Melting point: 198-199 ºC. IR (ν_{max}/cm^{-1}) 3037.0, 2910.0, 1634.9, 1591.6, 1574.7. ^{1}H-NMR (400 MHz, $CDCl_3$) 9.47 (brs, 1H), 8.25 (d, J=2.19 Hz, 1H), 8.10 (brs, 1H), 8.00 (d, J=8.38 Hz, 2H), 7.92 (d, J=3.28 Hz, 1H), 7.78 (d, J=0.56 Hz, 1H), 7.57 (d, J=4.64 Hz, 1H), 7.38 (d, J=8.18 Hz, 2H), 7.29 (m, 1H), 2,90 (s, 3H), 4.47 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) 149.73, 148.28, 146.30, 136.54, 133.98, 132.68, 132.58, 131.21, 130.40, 129.92, 128.58, 117.73, 115.42, 114.36, 106.58, 44.84, 21.97. HRMS (ESI) m/z calculated for $C_{19}H_{17}IN_2O_2S_2$ $(M-I)^+$: 369.0731, found: 369.0720.

*1-methyl-4-(naphthalen-2-yl)-6-tosyl-6H-pyrrolo[3,4-b]pyridin-1-ium iodide (**7h**).* Orange solid, 72% yield. Melting point: 112-113 ºC. IR (ν_{max}/cm^{-1}) 3053.7, 2920.5, 1634.0, 1590.6, 1574.9. ^{1}H-NMR (400 MHz, CD_3CN) 8.71 (d, J=5.88 Hz, 1H), 8.48 (d, J=1.67 Hz, 1H), 8.43 (d, J=2.45 Hz, 1H), 8.32 (d, J=2.45 Hz, 1H), 8.14 (m, 2H), 8.09 (d, J=8.53 Hz, 2H), 8.05 (d, J=1.53 Hz, 1H), 8.03 (d, J=1.22 Hz, 1H), 7.92 (dd, J=1.89, 8.56 Hz, 1H), 7.69 (m, 2H), 7.61 (d, J=5.92 Hz, 1H), 7.49 (d, J=8.04 Hz, 2H), 4.28 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, CD_3CN) 155.51, 150.05, 148.94, 135.32, 133.67, 133.56, 132.40, 131.37, 130.82, 130.49, 130.18, 129.83, 129.18, 129.06, 128.39, 127.98, 125.82, 120.08, 116.99, 116.86, 107.75, 44.72, 21.39. HRMS (ESI) m/z calculated for $C_{25}H_{21}IN_2O_2S$ $(M-I)^+$: 413.1323, found: 413.1323.

General procedure for Oxidation of Salts. To a stirred solution of salts in acetonitrile (0.2 M) was added potassium permanganate (2.2 equiv.) at room temperature. Upon addition, the reaction color changed from purple to dark brown. The reaction mixture was stirred for a couple of hours and then filtered through celite. The concentrated mixture was purified with preparative TLC using hexane and ethyl acetate (2:1) as mobile phase. The products were removed from silica gel by washing with dichloromethane and then methanol.

*1-methyl-4-phenyl-6-tosyl-1,6-dihydro-2H-pyrrolo[3,4-b]pyridin-2-one (**8a**).* White solid, 36% yield. Melting point: 115-116 ºC. IR (ν_{max}/cm^{-1}) 3130.6, 2924.4, 1637.3, 1595.4, 1552.7. ^{1}H-NMR (400 MHz, $CDCl_3$) 7.72 (d, J=8.42 Hz, 2H), 7.47 (m, 2H), 7.42 (m, 3H), 7.34 (d, J=2.35 Hz, 1H), 7.25 (dd, J=0.52 and 8.52 Hz, 2H), 6.87 (d, J=2.36 Hz, 1H), 6.34 (s, 1H), 3.35 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) 162.46, 145.85, 145.21, 136.36, 135.16, 133.09, 130.29, 129.65, 129.09, 127.58, 127.18, 119.02, 115.30, 115.13, 100.35, 30.21, 21.70. HRMS (ESI) m/z calculated for $C_{21}H_{19}N_2O_3S$ $(M+H)^+$: 379.1116, found: 379.1116.

*1-benzyl-4-phenyl-6-tosyl-1,6-dihydro-2H-pyrrolo[3,4-b]pyridin-2-one (**8b**):* White solid, 24% yield. Melting point: 74-75 ºC. IR (ν_{max}/cm^{-1}) 3136.4, 2952.4, 1647.5, 1590.4, 1542.0. ^{1}H-NMR (400 MHz, $CDCl_3$) 7.57 (d, J=8.41 Hz, 2H), 7.48 (m, 2H), 7.42 (m, 3H), 7.30 (d, J=2.34 Hz, 1H), 7.24 (m, 5H), 7.17 (d, J=8.41 Hz, 2H), 6.79 (d, J=2.35 Hz, 1 H), 6.51 (s, 1H), 5.11 (s, 2H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) 162.60, 146.26, 145.80, 136.12, 135.54, 134.99, 131.56, 130.19, 129.88, 129.14, 128.74, 128.51, 127.71, 127.54, 127.04, 118.19, 115.63, 115.26, 101.68, 47.47, 21.68. HRMS (ESI) m/z calculated for $C_{27}H_{17}N_2O_3S$ $(M+H)^+$: 455.1429, found: 455.1424.

*4-(4-methoxyphenyl)-1-methyl-6-tosyl-1,6-dihydro-2H-pyrrolo[3,4-b]pyridin-2-one (**8c**).* White solid, 32% yield. Melting point: 98-99 ºC. IR (ν_{max}/cm^{-1}) 3133.7, 2921.3, 1629.7, 1605.4, 1551.4, 1508.1, 1171.4. ^{1}H-NMR (400 MHz, $CDCl_3$) 7.72 (d, J=8.41 Hz, 2H), 7.44 (d, J=8.82 Hz, 2H), 7.35 (d, J=2.35 Hz, 1H), 7.24 (d, J=8.05 Hz, 2H), 6.94 (d, J=8.81 Hz, 2H), 6.85 (d, J=2.36 Hz, 1H), 6.29 (s, 1H), 3.81 (s, 3H), 3.34 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) 162.58, 160.82, 145.81, 144.75, 135.20, 133.18, 130.28, 128.90, 128.69, 127.16, 118.12, 115.31, 115.29, 114.49, 100.28, 55.44, 30.16, 21.70. HRMS (ESI) m/z calculated for $C_{22}H_{21}N_2O_4S$ $(M+H)^+$: 409.1222, found: 409.1211.

*4-(4-fluorophenyl)-1-methyl-6-tosyl-1,6-dihydro-2H-pyrrolo[3,4-b]pyridin-2-one (**8d**).* White solid, 29% yield. Melting point: 108-109 ºC. IR (ν_{max}/cm^{-1}) 3134.0, 2918.2, 1633.5, 1603.9, 1555.8. ^{1}H-NMR (400 MHz, $CDCl_3$) 7.73 (d, J=8.42 Hz, 2H), 7.47 (dd, J=5.27 and 8.83 Hz, 2H), 7.30 (d, J=2.35 Hz, 1H), 7.25 (dd, J=0.51 and 8.51 Hz, 2H), 7.12 (t, J=8.66 Hz, 2H), 6.87 (d, J=2.36 Hz, 1H), 6.30 (s, 1H), 3.35 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) 164.78, 162.30, 145.93, 144.15, 135.10, 133.00, 132.40, 132.36, 130.32, 129.43, 129.34, 127.19, 119.05, 116.30, 116.09, 115.06, 100.48, 30.23, 21.71. HRMS (ESI) m/z calculated for $C_{21}H_{18}FN_2O_3S$ $(M+H)^+$: 397.1022, found: 397.1010.

*4-(3,4-dichlorophenyl)-1-methyl-6-tosyl-1,6-dihydro-2H-pyrrolo[3,4-b]pyridin-2-one (**8e**).*White solid, 27% yield. Melting point: 146-147 °C. IR (ν_{max}/cm^{-1}) 3068.9, 2915.7, 1648.0, 1600.8, 1559.7. ^{1}H-NMR (400 MHz, $CDCl_3$) 7.74 (d, J=8.31 Hz, 2H), 7.56 (m ,2H), 7.50 (m, 2H), 7.30 (m, 2H), 7.27 (d, J=8.31 Hz, 2H), 6.92 (d, J=2.32 Hz, 1H), 6.45 (s, 1H), 3.39 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) 162.18, 136.00, 134.89, 134.17, 133.54, 131.21, 130.41, 130.27, 129.40, 128.33, 127.29, 126.82, 118.76, 114.96, 114.88, 114.54, 101.01, 29.71, 21.74. HRMS (ESI) m/z calculated for $C_{21}H_{17}Cl_2N_2O_3S$ $(M+H)^+$: 447.0337, found: 447.0334.

*1-methyl-4-(thiophen-2-yl)-6-tosyl-1,6-dihydro-2H-pyrrolo[3,4-b]pyridin-2-one (**8f**).* White solid, 31% yield. Melting point: 97-98 °C. IR (ν_{max}/cm^{-1}) 3108.2, 2921.4, 1632.7, 1595.4, 1551.2. ^{1}H-NMR (400 MHz, $CDCl_3$) 7.75 (dd, J=3.68 and 5.08 Hz, 2H), 7.61 (d, J=2.34 Hz, 1H), 7.41 (m, 2H), 7.26 (d, J=8.03 Hz, 2H), 7.11 (d, J=2.92 Hz, 1H), 6.86 (d, J=2.35 Hz, 1H), 6.49 (s, 1H), 3.34 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) 162.18, 145.92, 138.09, 137.56, 135.13, 133.08, 130.33, 128.15, 127.64, 127.20, 127.17, 117.66, 115.39, 114.21, 100.43, 30.20, 21.71. HRMS (ESI) m/z calculated for $C_{19}H_{17}N_2O_3S_2$ $(M+H)^+$: 385.0680, found: 382.0668.

*1-methyl-4-(naphthalen-2-yl)-6-tosyl-1,6-dihydro-2H-pyrrolo[3,4-b]pyridin-2-one (**8g**).* White solid, 33% yield; Melting point: 177-178 °C. IR (ν_{max}/cm^{-1}) 3005.8, 2956.4, 1654.8, 1618.0, 1555.8. ^{1}H-NMR (400 MHz, CD_3CN) 8.17 (d, J=1.27 Hz, 1H), 7.99 (m, 4H), 7.88 (d, J=8.44 Hz, 2H), 7.73 (q, J=8.60, 1.72 Hz, 1H), 7.58 (m, 4H), 7.39 (q, J=8.60, 0.60 Hz, 1H), 7.17 (d, J=2.39 Hz, 1 H), 6.42 (s, 1H), 3.37 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, CD_3CN) 162.29, 147.05, 145.51, 135.51, 134.28, 134.26, 133.87, 133.84, 130.88, 129.29, 129.10, 128.24, 127.83, 127.75, 127.64, 127.35, 125.87, 119.84, 116.17, 115.46, 101.64, 30.21, 21.23. HRMS (ESI) m/z calculated for $C_{25}H_{21}N_2O_3S$ $(M+H)^+$: 429.1273, found: 429.1263.

*1-methyl-4-phenyl-6-tosyl-1,6-dihydro-2H-pyrrolo[3,4-b]pyridin-2-one (**9**).* Light yellowish solid, 50% yield. Melting point: decomposed. IR (ν_{max}/cm^{-1}) 3170.2, 3062.1, 2923.4, 1615.3, 16, 1556.9. ^{1}H-NMR (400 MHz, $CDCl_3$) 8.70 (brs, 1H), 7.55 (m, 2H), 7.39 (m, 3H), 6.99 (m, 1H), 6.58 (m ,1H), 6.34 (s, 1H), 3.49 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) 162.23, 136.66, 129.96, 129.22, 129.01, 127.92, 127.49, 114.09, 111.88, 110.32, 100.45, 31.91. HRMS (ESI) m/z calculated for $C_{14}H_{13}N_2O$ $(M+H)^+$: 225.1028, found: 225.1020.

ACKNOWLEDGEMENTS

We acknowledge the generous support of National Science Foundation Catalyst Program (1956269). Also, we would like to thank Winston Salem State University National Institute of General Medical Sciences (NIGMS) RISE Program (R25GM113774) for financial help.

REFERENCES

(1) Synthesis of isoindoles and related iso-condensed heteroaromatic pyrroles. Heugebaert, T. S. A.; Roman, B. I.; Stevens, C. V. *Chem. Soc. Rev*., **2012**, *41*, 5626.

(2) (a) Syntheses of Iso-Condensed Heteroaromatic Pyrroles. C. K. Sha, C. P. Tsou, C. Y. Tsai, J. M. Liu, R. S. Lee, Y. C. Li, F. Y. Tsai, S. J. Way, J. J. Young, K. S. Chuan and R. H. Yeh*, J. Chin. Chem. Soc*. (Taipei), **1992**, *39*, 635–639.
(b) Orthogonal Synthesis of Isoindole and Isoquinoline Derivatives from Organic Azides. B. W.-Q. Hui and S. Chiba, *Org. Lett*., **2009**, *11*, 729–732.

(3) Synthesis and Diels-Alder reactions of furo [2, 3-c] pyrroles and benzofuro [2, 3-c] pyrroles. C. K. Sha, R. S. Lee and Y. Wang, *Tetrahedron*, **1995**, *51*, 193–202.

(4) Aza-isoindolo and isoindolo-azaquinoxaline derivatives with antiproliferative activity. Parrino, B.; carbone, A.; Spano, V.; Montalbano, A.; Giallombardo, D.; Barraja, P.; Attanzio, A.; Tesoriere, L.; Sissi, C.; Palumbo, M.; Cirrincione, G.; Diana, P. *Eur. J. Med. Chem*. **2015**, *94*, 367-377.

(5) Gold-Catalyzed Waste-Free Generation and Reaction of Azomethine Ylides: Internal Redox/Dipolar Cycloaddition Cascade. H.-S. Yeom, J.-E. Lee and S. Shin, *Angew. Chem., Int. Ed.*, **2008**, *47*, 7040–7043.

(6) The reaction of arynes with münchnones: synthesis of isoindoles and azaisoindoles. Lopchuk,J. M.; Gribble, G.W. *Tet. Lett*. **2014**, *55*, 2809-2812.

(7) (a) Synthesis of substituted pyridines from 1, 2-nucleophilic addition products of functionalized N-acyl-2, 3-dihydropyridones. Guzel, M.; Watts, J.; McGilvary, M.; Wright, M.; Kiren, S. *Tetrahedron Lett*. **2015**, *56*, 5275-5277.
(b) Pyrroles from TosMIC and substituted N-acyl-2, 3-dihydro-4-pyridones: A short access to a 4-azaisoindole unit. **Kiren. S**.; Brooks, A. M.; Graves, J. J. *Tetrahedron Lett*. **2019,** *60(22)*, 1490-1492.

(8) (a) Pyridinium salts: from synthesis to reactivity and applications. Sowmiah, S.; Esperanca, J. M. S. S.; Rebelo, L. P. N.; Afonso, C. A. M. *Org. Chem. Front*. **2018**, *5*, 453.
(b) Synthesis and Biological Activity of Quaternary Quinolinium Salts: A Review. Utreja, D.; Sharma, S.; Goyal, A.; Kaur, K.; Kaushal, S. *Curr. Org. Chem*. **2019**, *23*, 2271-2294.
(c) Synthesis and crystal structure of quinolinium salt: Assignment on nonsteroidal anti-inflammatory activity and DNA cleavage activity. Singh, P.; Kumar, R.; Singh, A. K.; Yadav, P.; Khanna, R. S.; Vinayak, M.; Tewari, A. K. *J. Mol. Struct*. **2018**, *1163*, 262-269.
(d) Solution, Thermal, and Optical Properties of Poly(pyridinium salt)s Derived from an Ambipolar Diamine Consisting of Diphenylquinoline and Triphenyl Amine Moieties. Nedeltchev, A. K.; Han, H.; Bhowmik, P. K. J. *Polym. Sci. A Polym. Chem*. **2010**, *48*, 4611–4620.
(e) Facile synthesis and photophysical characterization of new quinoline dyes. Santos, G. C. D.; Andrade Bartolomeu, A. de; Ximenes, V. F.; da Silva-Filho, L. C. *J. Fluoresc*. **2017**, *27*, 271–280.

(9) (a) 4-Hydroxy-2-pyridone alkaloids: structures and synthetic approaches. H. J. Jessen, K. Gademann, *Nat. Prod. Rep.* **2010**, *27*, 1168.
(b) Approaching a stable, green twisted heteroacene through “clean reaction” strategy. G. Li, H. M. Duong, Z. Zhang, J. Xiao, L. Liu, Y. Zhao, H. Zhang, F. Huo, S. Li, J. Ma, F. Wudl, Q. Zhang, *Chem. Commun.* **2012**, *48*, 5974.

(c) Pyridones–Powerful Precursors for the Synthesis of Alkaloids, Their Derivatives, and Alkaloid-Inspired Compounds. Sosnicki, J. G.; Idzik, T. J. *Synthesis* **2019**, *51*, 3369-3396.
(d) Construction of fully substituted 2-pyridone derivatives via four-component branched domino reaction utilizing microwave irradiation. Bai, H.; Sun, R.; Liu, S.; Yang, L.; Chen, X.; Huang, C. *J. Org. Chem*. **2018**, *83*, 12535−12548.
(e) 2-Pyridone-functionalized Aza-BODIPY photosensitizer for imaging-guided sustainable phototherapy. Xiao, W.; Wang, P.; Ou, C.; Huang, X.; Tang, Y.; Wu, M.; Si, W.; Shao, J.; Huang, W.; Dong, X. *Biomaterials* **2018**, *183*, 1-9.
(f) Pyridine-Fused 2-Pyridones via Povarov and A^3 Reactions: Rapid Generation of Highly Functionalized Tricyclic Heterocycles Capable of Amyloid Fibril Binding. Singh, P.; Edolfsson, D. E.; Ade, J.; Cairns, A. G.; Bartens, C.; Brannstrom, K.; Olofsson, A.; Almqvist, F. *J. Org. Chem*. **2019**, *84*, 3887−3903.
(g) New synthetic methods to 2-pyridone rings. M. Torres, S. Gil and M. Parra, *Curr. Org. Chem*., **2005**, *9*, 1757–1779.

(10) (a) One-pot copper-catalyzed three-component reaction: a modular approach to functionalized 2-quinolones. Kim, A. R.; Lim, H. N. *RSC Adv.*, **2020**, *10*, 7855-7866.
(b) Cationic Pd (II) catalyzed regioselective intramolecular hydroarylation for the efficient synthesis of 4-aryl-2-quinolones. Singh, K.; Malviya, B. K.; Verma, V. P.; Badsara, S. S.; Bhardwaj, V. K.; Sharma, S. *Tetrahedron*, **2019**, *75*, 2506-2520.
(c) Palladium-catalysed synthesis and transformation of quinolones. Silva, V. L. M.; Silvaa, A. M. S. *Molecules* **2019**, *24*, 228.
(d) Recent advances in the synthetic and medicinal perspective of quinolones: A review. Dhiman, P.; Arora, N.; Thanikachalam, P. V.; Monga, V. M. *Bioorg. Chem*. **2019**, *92*, 103291.
(e) Oxidative Aromatization of 3,4-Dihydroquinolin-2(1H)-ones to Quinolin-2(1H)-ones Using Transition-Metal-Activated Persulfate Salts. Chen, W.; Sun, C.; Zhang, Y.; Hu, T.; Zhu, F.; Jiang, X.; Abame, M. A.; Yang, F.; Suo, J.; Shi, J.; Shen, J.; Aisa, H. A. *J. Org. Chem*. **2019**, *84*, 8702−8709.
(f) Quinolone hybrids and their anti-cancer activities: An overview. Gao, F.; Zhang, X.; Wang, T.; Xiao, J. *Eur. J. Med. Chem*. **2019**, *165*, 59-79.

(11) (a) Convenient Route to 2H-Pyrrolo[3,4-b]quinolin-9(4H)-one Skeleton via TosMIC Reaction. Rosi, F.; Crucitti, G. C.; Iacovo, A.; Miele, G.; Pescatori, L.; Santo, R. D.; Costi, R. *Synth. Commun*. **2013**, *43*, 1063.
(b) Novel pyrrolyllactone and pyrrolyllactam indolinones as potent cyclin-Dependent kinase 2 inhibitors. Li, X.; Huang, P.; Cui, J. C.; Zhang, J.*;* Tang, C. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1939.
(c) Synthesis of 3, 4-fused cycloalkanopyrroles by 1, 3-dipolar cycloaddition. Kelly, J. M.; Leeper, F. J. *Tetrahedron Lett.* **2012**, *53*, 819.
(d) An Expeditious Synthesis of Pyrrolo [3, 4-d] pyrimidine-2, 4-dione from Uracil. Zimmerman, M. N.; Nemeroff, N. H.; Bock, C. W.; Bhat, K. L. *Heterocycles* **2000**, *53*, 205.

(12) Synthesis and oxidative aromatization of 3, 5-disubstituted-2- pyrazolines by $Ce(SO_4)_2.4H_2O$ as a convenient oxidizing agent. Kumbhar, D. D.; Waghamare, B. Y.; Lokhande, P. D.; Pardeshi, S. K. *Res. J. Pharm. Biol. Chem. Sci.* **2014**, *5*, 727.

(13) An efficient route to N-alkylated 3, 4-dihydroisoquinolinones with substituents at the 3-position. Tazawa, A.; Ando, J.; Ishizawa, K.; Azumaya, I.; Hikawa, H.; Tanaka, M *RSC Adv*., **2018**, *8*, 6146.

(14) An organocatalyst bound α-aminoalkyl radical intermediate for controlled aerobic oxidation of iminium ions. Motaleb, A.; Bera, A.; Maity, P. *Org. Biomol. Chem*. **2018**, *16*, 5081.

(15) Base-promoted aerobic oxidation of N-alkyl iminium salts derived from isoquinolines and related heterocycles. Bai, Li-Gang; Zhou, Yue; Zhuang, Xin; Zhang, Liang; Xue, Jian; Lin, Xiao-Long; Cai, Tian; Luo, Qun-Li *Green Chem*. **2020**, *22*, 197.

(16) Ultrasound-Promoted Synthesis of Quinolone and Isoquinolone Derivatives. M. G.-Dubois, M.; Meola, A., *Synth. Commun*. **1995**, *25*, 2999.

(17) (a) Bioinspired syntheses of the pyridoacridine marine alkaloids demethyldeoxyamphimedine, deoxyamphimedine, and amphimedine. Khalil, I. M.; Barker, D.; Copp, B. R. *J. Org. Chem*. **2016**, *81*, 282−289.
(b) Expanded π-electron systems, tri (phenanthro) hexaazatriphenylenes and tri (phenanthrolino) hexaazatriphenylenes, that are self-assembled to form one-dimensional Aggregates. Ishi-i, T.; Hirashima, R.; Tsutsumi, N.; Amemori, S.; Matsuki, S.; Teshima, Y.; Kuwahara, R.; Mataka, S. *J. Org. Chem.* **2010**, *75*, 6858−6868.
(c) An Enantioselective Access to 1-Alkyl-1, 2, 3, 4-tetrahydroisoquinolines. Application to a New Synthesis of (−)-Argemonine. Youte, J.-J.; Barbier, D.; Al-Mourabit, A.; Gnecco, D.; Marazano, C. *J. Org. Chem*. **2004**, *69*, 2737−2740.
(d) Synthesis of phenanthridine skeletal Amaryllidaceae alkaloids. Fan-Chiang, T.-T.; Wang, H.-K.; Hsieh, J.-C. *Tetrahedron* **2016**, *72*, 5640−5645.
(e) Synthesis of tetrahydroquinolines, hexahydrobenzoindolizines and an aryl phosphonate linker for the generation of catalytic antibodies. G.-Bello, C.; Abell, C.; Leeper, F. J. J. *Chem. Soc. Perkin Trans. 1*, **1997**, 1017-1024.

(18) Carbene-catalyzed aerobic oxidation of isoquinolinium salts: efficient synthesis of isoquinolinones. Wang, G.; Hu, W.; Hu, Z.; Zhang, Y.; Yao, W.; Li, L.; Fu, Z.; Huang, W. *Green Chem*., **2018**, *20*, 3302.

(19) Synthesis of 3,4-dihydroisoquinolines, 2-alkyl(Acyl)-1(2H)-3,4-dihydroisoquinolinones, 2-alkyl-1(2H)-isoquinolinones and 1-alkyl-2(2H)-quinolinones by oxidation with potassium permanganate. Venkov, A. P.; S.-Abeghe, S. M. *Tetrahedron*, **1996**, *52*, 1451-1460.