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Intramolecular Oxidative Arylations in 7-Azaindoles and Pyrroles: Revamping the Synthesis of Fused *N*-Heterocycle Tethered Fluorenes

Joydev K. Laha,* Rohan A. Bhimpuria, and Mandeep Kaur Hunjan

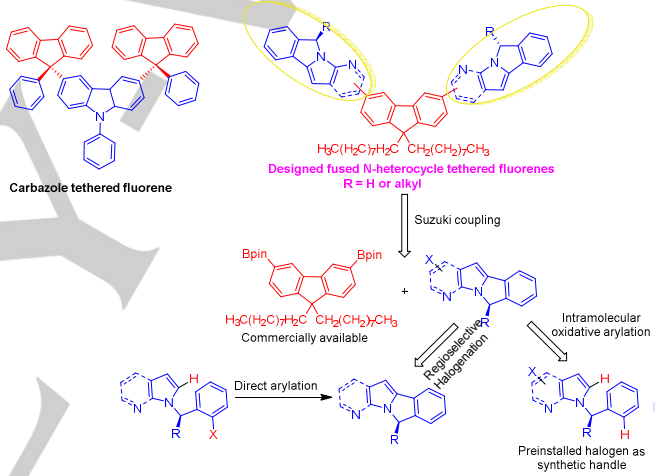
Abstract: The report unveils intramolecular oxidative arylations in 7-azaindoles and pyrroles for the first time providing a direct access to 7-azaindoles or pyrroles fused isoindolines and tetrahydroisoquinolines. In addition, N-benzylation of 7-azaindoles or pyrroles with sterically hindered *sec*-benzyl alcohols by Mitsunobu reaction followed by intramolecular oxidative arylation allowed access to chiral congeners of fused isoindolines that have rare literature precedence. A new opportunity in the design and synthesis of fluorene based organic emitters is demonstrated in the preparation of novel fused *N*-heterocycle tethered fluorenes including a chiral fluorene architecture.

Introduction

The growing utilization of fused nitrogen heterocycles in the synthesis of single fluorene based organic fluorescent materials for potential use in organic light emitting devices (OLEDs) has become a current trend of research in organic electronics.[1] Many single fluorene molecule based organic emitters currently available fall short of desirable properties, namely, a specific emission, high charge-carrier mobility, good thermal and electrochemical stability, high photoluminence quantum yield, and facile chemical modification.[2] The attenuation of several desirable properties is improved in many folds by tethering a fused nitrogen heterocycle onto the fluorene backbone (Scheme 1).[3]

Structurally related 7-azaindole, indole, and pyrrole fused isoindolines possess electronic properties that significantly differ from one to the other by virtue of the electronic properties of the nitrogen heterocycle fused with isoindolines, with pyrrole being the most electron-rich and 7-azaindole being the electron-deficient.[4] While the synthesis of indole fused isoindolines and their use in materials sciences are self-evident,[5] the related 7-azaindole or pyrrole fused isoindolines appears to be captive for similar applications.[6] Indeed, 7-azaindole or pyrrole fused isoindolines incorporated into the fluorene backbone could lead to extensive designing of new fluorescent organic materials (Scheme 1). A blueprint of fluorene architecture that has a substituent at the benzylic position, largely to stop adventitious benzylic oxidation, is also feasible. The designed targets could be prepared by Suzuki reaction of the commercially available 9,9-dioctyl-9*H*-fluorene-2,7-diboronic acid bis(pinacol) ester and fused isoindolines containing a preinstalled halogen.

However, the preparation of these newly designed organic materials could present excessive challenge, as halo-substituted 7-azaindole or pyrrole fused isoindolines have rarely been synthesized. As the retrosyntheic analysis reveals, the halo-



Scheme 1. Retrosynthetic Design of Fused *N*-Heterocycle Tethered Fluorenes

substituted fused isoindolines could, in principle, be obtained either by regioselective halogenation of the corresponding fused isoindolines, or intramolecular oxidative arylation in 7-azaindoles or pyrroles containing a preinstalled halogen. 7-Azaindole or pyrrole fused isoindolines have traditionally been synthesized using transition metal-catalyzed intramolecular direct or cross coupling reactions.[7] Although a few reports of intramolecular oxidative couplings including a pioneering study by Greaney et al.,[8d] largely in 3-substituted indoles yielding medium ring fused indoles, and subsequently by Bao,[8c] Guo,[8b] and DeBoef[8a] in benzimidazoles and purines affording benzimidazole fused isoindolines are available, they are limited to the nitrogen heterocycles that have a substituent[8d] or nitrogen[8a-c] at the 3-position, and perhaps more importantly, lacking demonstration of the preparation of a halogen-installed fused isoindolines. The underlying difficulties of implementing an intramolecular oxidative arylation in 7-azaindoles and pyrroles could explain the lack of literature precedence.

Based on this thematic background, we embarked on an objective aimed at developing an intramolecular oxidative arylation in 7-azaindoles and pyrroles that could meet the

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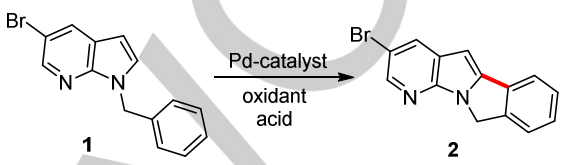
preparative challenges of newly designed organic materials. The underlying challenges in developing an intramolecular oxidative coupling in 7-azaindoles and pyrroles would include: a) limited literature precedence for regioselective halogenations in 7-azaindoles,[9a] especially at the 3-position, b) untoward intermolecular reaction,[8a] dehalogenation,[7d,9b] or potential oxidation at the benzylic position[7d] that could occur during intramolecular oxidative arylations in 7-azaindoles or pyrroles containing a preinstalled halogen, and c) ability of pyridine nitrogen in 7-azaindoles to co-ordinate with palladium.[10] To resolve the cumulative challenge, the following measure were taken into consideration: a) regioselective bromination of 7-azaindoles under a mild condition, b) a judicious choice of oxidant that could selectively effect intramolecular oxidative arylation without affecting the benzylic position, c) a high acid concentration could largely suppress the nucleophilicity of pyridine nitrogen, and d) a careful choice of the acid to avoid any potential reaction of the nucleophilic carboxylate anion. Leveraging our previous experiences on oxidative C–C bond formation in the synthesis of biaryl sultams,[11] heterobiaryl sultams, [12] 4-azafluorenones, [13] carbazoles and α-carbolines, [14] and C-2 arylated heterocycles,[15] we surmised that an intramolecular oxidative arylation in 7-azaindoles and pyrroles while an ambitious objective would be a distinct, straightforward gateway to the synthesis of fused isoindolines. Herein, we describe intramolecular oxidative arylations in 7-azaindoles and pyrroles providing a direct access to 7-azaindoles or pyrroles fused isoindolines including fused isoindolines containing a stereocenter α to nitrogen and tetrahydroisoquinolines. The pivotal to the success with oxidative arylations was a critical acid concentration. The preparation of fused *N*-heterocycle tethered fluorenes including a chiral fluorene is also demonstrated warranting broad application of this protocol.

Results and Discussion

Our initial investigation was largely focused on identifying a reaction condition that could effect intramolecular cyclization of 5-bromo-*N*-benzyl-7-azaindole (**1**) lacking a 3-substituent to furnish 7-azaindole fused isoindolines **2** under oxidative conditions. Thus, when **1** was heated in the presence of $Pd(OAc)_2$ (10 mol%), AgOAc (3 equiv), and PivOH (125 mM) at 130 ℃ for 12 h, compound **2** was isolated, however, only in 37% yield (Table 1, entry 1). The intramolecular cyclization when performed in a mixture of PivOH and other solvent, e.g., MeCN, DMF, DMSO, or DCE at higher dilution proved to have a deleterious effect as no product formation was observed in any case (entries 2-4). To our delight when PivOH was used as the only solvent (625 mM), **2** was obtained in 69% isolated yield (entry 5). The other acid such as acetic acid had adverse effect in the reaction (entry 6). A stronger oxidant such as $K_2S_2O_8$ did not give any product (entry 7). A palladium (0) catalyst was less effective (entry 8). Central to this investigation was the observation that a high pivalic acid concentration in the reaction medium was essential for successful intramolecular oxidative arylation. The key features of intramolecular oxidative arylations as enumerated are: a) debromination of **1** or **2** did not occur under the optimized conditions, b) the nucleophilicity of pyridine nitrogen is largely suppressed in the presence of high acid concentrations avoiding catalyst poisoning, c) any product corresponding to benzylic oxidation was not observed.

Next, we investigated the scope of substituted 7-azaindoles and pyrroles that could participate in the intramolecular oxidative arylation (Scheme 2). The preparation of starting substrates **3-11** that participated in the intramolecular cyclization is detailed in the Supporting Information. During the preparation of starting materials, a regioselective bromination of 7-azaindole **3** and pyrrole **9a** was developed under mild conditions, which produced 3-bromo-7-azaindole **5** and **9b**, respectively, in excellent yields. 7-Azaindoles and C-2 substituted pyrroles containing various electron-donating or -withdrawing groups were viable substrates and reacted eventfully yielding diversely substituted fused isoindolines **12-20**. However, unsubstituted *N*-benzylpyrrole (**11a**) or pyrrole containing an electron donating C-2 substituent (for example, **11b**) did not give the corresponding intramolecular cyclization products **20a**-**20b** under optimized conditions. Notably, compatibility of the functional groups such as aryl, halogen, -OMe, -CHO, CO_2Me, CF_3, etc. used in this study is noteworthy. A mixture of regioisomers was obtained when azaindole **8** was subjected to the optimized conditions. The major regioisomer was formed in the intramolecular cyclization occurred at the *para*-position of OMe group.

Table 1. Optimization Study[a]



1 2

Entry	Catalyst	Oxidant	Acid	Solvent	%2[b]
1[c]	$Pd(OAc)_2$	AgOAc	PivOH	-	37
2[c]	$Pd(OAc)_2$	AgOAc	PivOH	MeCN	00
3[c]	$Pd(OAc)_2$	AgOAc	PivOH	DMF/ DMSO	00
4[c],[d]	$Pd(OAc)_2$	AgOAc	PivOH	DCE	00
5	$Pd(OAc)_2$	AgOAc	PivOH	-	69
6	$Pd(OAc)_2$	AgOAc	AcOH	-	21
7	$Pd(OAc)_2$	$K_2S_2O_8$	PivOH	-	00
8	$Pd(PPh_3)_4$	AgOAc	PivOH	-	57

[a] Substrate (0.25 mmol), catalyst (10 mol%), oxidant (3 equiv), solvent (4 mL), 130 °C, 12 h; [b] Isolated yield; [c] PivOH (2 mL), other solvent, (if any, 2 mL) for entries 2-4; [d] Temp. 90 °C.

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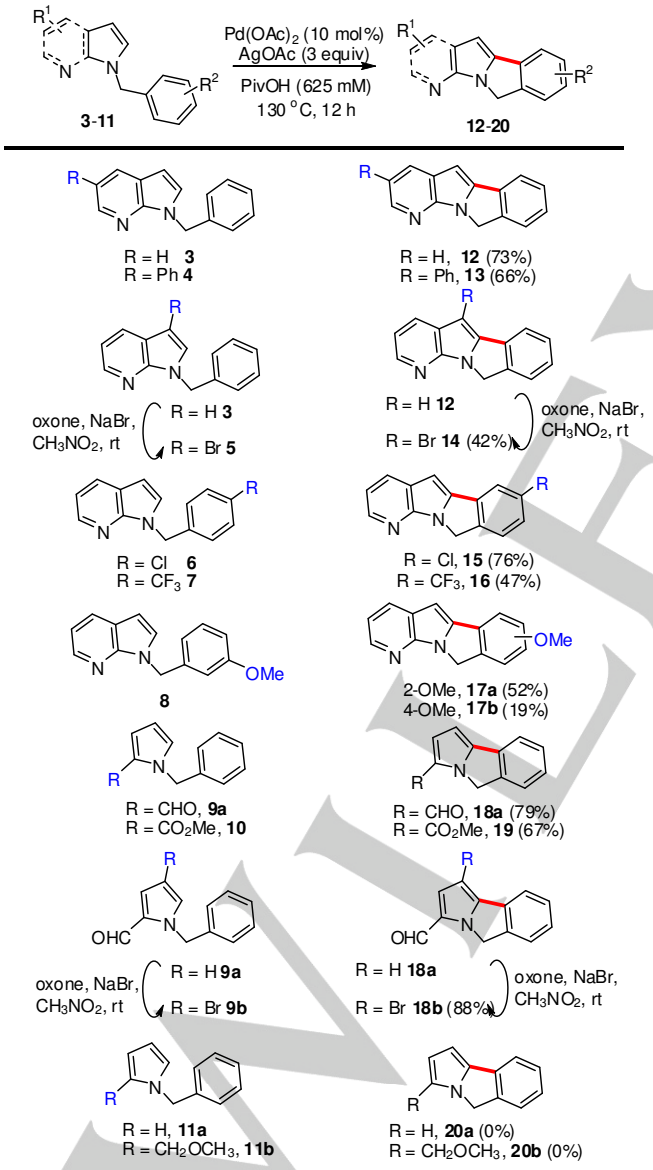
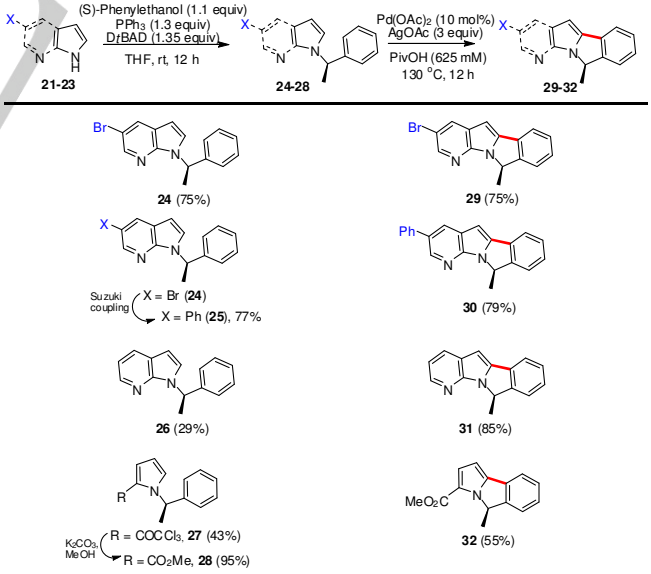
Bromination of compounds **12** and **18a** using the mild conditions described above gave compounds **14** and **18b** demonstrating the versatility of the brominating agent used in this study. Notably, the regioselective bromination of fused isoindolines was previously unknown. Although the compounds **14** and **18b** were preparaed from **12** and **18a**, respectively, the brominated heterocycles **5** and **9b** could potentially serve as precursors to them. It is important to note here that a bromo group in compounds **14** and **18b** could serve as synthetic handle for further functionalizations. Taken together, only a few of these fused isoindolines are available in literature, which have been prepared using prefunctionalized substrates via direct arylation or cross-coupling reactions. Distinct from the current literature,[8] our protocol does not require any C-3 substituent in nitrogen heterocycles.



Scheme 2. Substrate Scope for Intramolecular Oxidative Cyclization.

Next, we investigated the synthesis of *N*-heterocycle fused chiral isoindolines that have poor literature precedence.[7e] Perhaps most importantly, their preparation using intramolecular oxidative coupling has not hitherto been reported. This prompted us to explore their synthesis under the optimized conditions. The starting substrates for intramolecular cyclizations were prepared from the corresponding nitrogen heterocycles via Mitsunobu reaction, which readily installed a stereocenter α to nitrogen. Reaction of 7-azaindoles or 2-trichloracetylpyrrole with an optically pure *sec*-benzyl alcohol under Mitsunobu condition gave the products either ready for intramolecular cyclization, or further functionalization followed by cyclization. The optical purity of the N-alkylated 7-azindole **24**, obtained after Mitsunobu reaction, was assessed by chiral HPLC. For this purpose, Mitsunobu reaction of 7-azaindole **24** and racemic sec-alcohol was performed. A method was developed to resolve the enantiomers in the racemic maixture. It was found that the 7-azindole **24** obtained in our study showed only one peak (see ESI). Notably, such Mitsunobu reactions of 7-azaindoles are currently unavailable in the literature. So, when **24-28** were subjected to the optimized condition, all of them reacted smoothly to deliver the cyclized products **29-32** in good to excellent yields (Scheme 3). Pivotal to this study was unveiling intramolecular oxidative arylations in 7-azaindoles and pyrroles yielding chiral fused isoindolines with a defined stereocenter.

7-Azaindole or pyrrole fused tetrahydroisoqunolines are important class of nitrogen heterocycles exhibiting diverse biological profiles.[16] These compounds have invariably been synthesized by direct arylations using prefunctionalized substrates.[17]



Scheme 3. Fused Isoindolines with a Defined Stereocenter.

To demonstrate further generality of our protocol, *N*-alkyl 7-azaindole **33** and pyrrole **34** were exposed to the optimized conditions. The intramolecular oxidative arylations occurred

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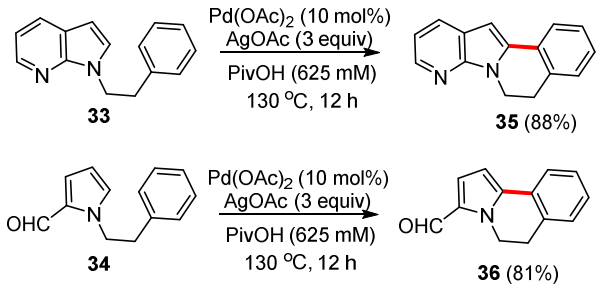
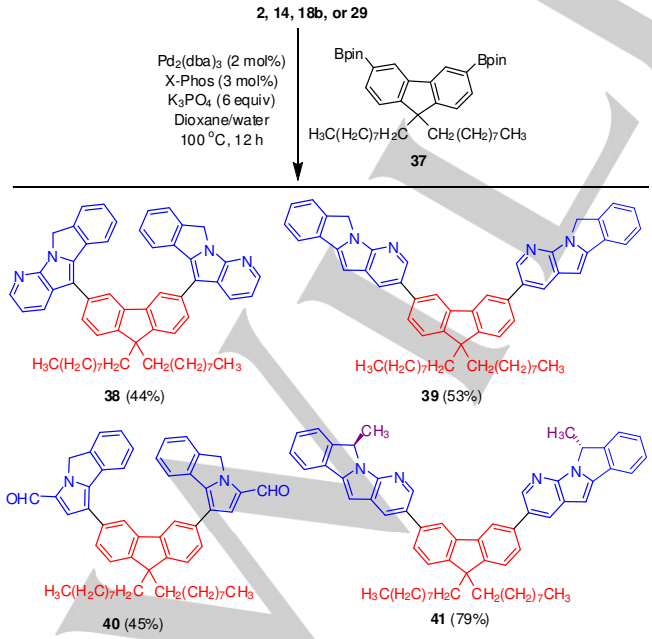
smoothly both in **33** and **34** affording fused tetrahydroisoquinolines **35** and **36** in 88 and 81% yields, respectively (Scheme 4).



Scheme 4. Synthesis of Fused Tetrahydroisoquinolines.

Thus, our protocol is clearly distinct from the literature protocols in terms of general applicability warranting preparation of both fused isoindolines and tetrahydroisoquinolines.

To demonstrate a translational application of our newly developed protocol, we prepared fluorene based organic molecules **38-41** tethered with fused isoindolines **2, 14, 18b,** and **29**. Thus, reaction of **2, 14, 18b,** or **29** and 9,9-dioctyl-9*H*-fluorene-2,7-diboronic acid bis(pinacol) ester (**37**) under Suzuki conditions gave novel fused *N*-heterocycle tethered fluorenes **38-41** (Scheme 5). The fluorene backbone is tethered with a fused heterocycle either at 3- or 5-position of the heterocycle. More importantly, the successful preparation of the designed fluorenes including a chiral fluorene architecture not only features their novelty, but also augurs a strong impetus towards finding their applications in OLEDs.



Scheme 5. Preparation of Novel Fused *N*-heterocycle Tethered Fluorenes.

The photoluminescence spectra of these fluorenes are provided in the Supporting Information. The detailed photophysical properties of these organic materials will be reported elsewhere. This preliminary study could open a new avenue for the preparation of single fluorene based fluorescent organic materials for potential use in OLEDs.

Conclusions

In conclusion, we have developed a novel approach for the intramolecular oxidative arylations in 7-azaindoles and pyrroles providing a direct access to 7-azaindoles or pyrroles fused isoindolines and tetrahydroisolquinolines. The high acid concentration in the reaction medium was the key to the successive development of the protocol. Reaction of 7-azaindoles or pyrroles and sterically hindered optically pure *sec*-benzyl alcohols under Mitsunobu condition followed by intramolecular oxidative arylation of N-benzyl-7-azaindoles or pyrroles allowed access to optically pure novel fused isoindolines. A new opportunity in the design and synthesis of single fluorene based organic emitters is demonstrated in the preparation of fused *N*-heterocycle tethered fluorenes. The detailed photophysical properties of these organic materials are currently under investigation.

Experimental Section

General procedure for palladium catalyzed intramolecular oxidative coupling

To an oven-dried schlenk tube was charged with 7-azaindole/pyrrole substrate (0.25 mmol), Pd(OAc)2 (10 mol%), AgOAc (3 equiv) and Pivalic acid (4 mL). Reaction mixture was then heated at 130 °C for 12 h. Following which it was cooled to room temperature and saturated solution of sodium carbonate (20 mL) was added. It was then extracted with EtOAc (2 x 20 mL), organic layer was concentrated under reduced pressure followed by chromatography [silica, EtOAc-hexanes = 2:8 ~ 2.5:8.5] to give cyclized product in good yields.

General procedure for Suzuki coupling for the synthesis of 38-41

37 (0.1 mmol), Substrate **2**, **14**, **18b** or **29** (2.2 equiv), $Pd_2(dba)_3$ (2 mol%) X-Phos (3 mol%) and K_3PO_4 (6 equiv) in 1,4-dioxane:water (4 mL, 3:1 mixture) was heated at 100 °C for 12 h. The reaction mixture was allowed to cool to room temperature, diluted with EtOAc (5 mL) and was concentrated under vacuum. The residue product was purified by silica gel column chromatography (hexane/EtOAc, 96:4) to give **38-41** in good yield.

General Procedure for *N*-benzylation of 7-azaindoles and pyrroles

Following a literature procedure[15], a dried round bottom flask equipped with a magnetic stirrer bar was charged with 7-azaindole/pyrrole (2 mmol) and THF (5 mL). The reaction mixture was cooled down to 0 °C and NaH (1.2 equiv) was added. After that alkyl halide (1.2 equiv) was added and continued the stirring for 4-6 h. After completion of the reaction it was quenched with water (10 mL) and was extracted with ethyl acetate (3 x 20 mL). The combined organic layer was dried over Na_2SO_4

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and the solvent was removed under reduced pressure followed by chromatography [silica, EtOAc-hexanes = 0.1:9.9 ~ 0.5:9.5] gave corresponding *N*-alkylated heterocycle in good yields.

General procedure for Regioselective Bromination of 3, 12, 18a, 19[18]

To an oven dried round bottom flask equipped with magnetic stir bar was charged with **3, 9a, 12, or 18a** (1 mmol), NaBr (1.1 equiv) and oxone® (1.2 equiv) and then nitromethane (2 mL) was added. Reaction mixture was allowed to stir 20 min- 24 h depending on substrate to give corresponding C-3 brominated products **5**, **11**, **14** and **18b** in good to moderate yields.

General procedure for MItsunobu reaction[7e]

Following a literature procedure[2], an oven-dried round bottom flask equipped with a magnetic stir bar was charged with 7-azaindole/pyrrole substrate (1 mmol) and triphenylphosphine (1.3 equiv), following which nitrogen was flushed three times and anhydrous THF (3 mL) was added. Then, (S)-phenylethanol (1.1 equiv) dissolved in anhydrous THF (2 mL) was added dropwise under nitrogen atmosphere. Then, Di-*tert*-butylazodicarboxylate (DtBAD) (1.35 equiv) dissolved in anhydrous THF (2 mL) was added under nitrogen atmosphere. Then, reaction was allowed to continue overnight. After that, diethyl ether was added and reaction mixture was stirred for 1 hr which was then filtered and filtrate was concentrated under reduced pressure followed by chromatography [silica, EtOAc-hexanes = 0.1:9.9 ~ 0.5:9.5] gave corresponding *N*-alkylated heterocycle in good yields.

Characterization Data for selected compounds

10*H*-Pyrido[3', 2':4,5]pyrrolo[2,1-*a*]isoindole (2)

Brownish solid, (48 mg, 69%). mp 177-178 °C; IR (ATR, cm^{-1}): 2930, 1591, 1331, 1100; ^{1}H NMR ($CDCl_3$): δ 8.28 (s, 1H), 8.03 (d, J = 1.9 Hz, 1H), 7.75 (d, J = 7.4 Hz, 1H), 7.53(d, J = 7.4 Hz, 1H), 7.47-7.38 (m, 2H), 6.52 (s, 1H), 5.19 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 145.7, 143.8, 142.6, 141.9, 131.8, 131.1, 128.3, 128.3, 126.9, 123.9, 121.4, 111.6, 89.2, 48.0; HRMS (ESI) m/z calcd for $C_{14}H_{10}BrN_2$ $[M+H]^+$ 285.0027, found 285.0022.

(R)-3-Bromo-10-methyl-10*H*-pyrido[3',2'4,5] pyrrolo[2,1-*a*]isoindole (29): Colorless liquid, (56 mg, 75%); Specific rotation $[\alpha]_{589}$ = -56; IR (ATR, cm^{-1}): 2923, 1450, 878, 741; ^{1}H NMR ($CDCl_3$): δ 8.30 (d, J = 2.0 Hz, 1H), 8.05 (d, J = 2.1 Hz, 1H), 7.75 (d, J = 6.9 Hz, 1H), 7.49-7.39 (m, 3H), 6.51 (s, 1H), 5.52 (q, J = 6.7 Hz, 1H), 1.88 (d, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 149.5, 148.0, 144.6, 144.0, 142.6, 130.9, 130.9, 128.3, 127.2, 123.0, 121.3, 111.6, 89.0, 56.7, 19.8; HRMS (ESI) m/z calcd for $C_{15}H_{12}BrN_2$ $[M+H]^+$ 299.0184, found 299.0179.

5,6-dihydropyrido[3',2':4,5]pyrrolo[2,1-*a*]isoquinoline (35): Yellow liquid, (44 mg, 88%); IR (ATR, cm^{-1}): 2850, 2820, 1455; ^{1}H NMR ($CDCl_3$): δ 8.32 (d, J = 4.6 Hz, 1H), 7.92 (d, J = 7.7 Hz, 1H), 7.80 (d, J = 7.5 Hz, 1H), 7.36-7.28 (m, 3H), 7.09-7.06 (m, 1H), 6.81 (s, 1H), 4.51 (t, J = 6.6 Hz, 2H), 3.23 (t, J = 6.5 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 147.8, 142.6, 135.9, 133.2, 128.5, 128.4, 128.3, 128.1, 127.2, 124.4, 121.6, 116.1, 94.2, 38.6, 28.9; HRMS (ESI) m/z calcd for $C_{15}H_{13}N_2$ $[M+H]^+$ 221.1079, found 221.1077.

5,5'-(9,9-dinonyl-9H-fluorene-3,6-diyl)bis(10H-pyrido[3',2':4,5]pyrrolo [2,1-a]isoindole (38): Yellow solid; (36 mg, 44%); mp 177-178 °C; IR (KBr, cm^{-1}): 2850, 1599, 1478, 1280, 1010, 994; ^{1}H NMR ($CDCl_3$): δ (8.39 (d, J = 3.9 Hz, 2H), 8.19 (dd, J = 7.9, 1.3 Hz, 2H), 7.96-7.93 (m, 4H), 7.75-7.73 (m, 4H), 7.62 (d, J = 7.3 Hz, 2H), 7.43-7.33 (m, 4H), 7.19-7.16 (m, 2H), 5.36 (s, 4H), 2.17-2.13 (m, 4H), 1.15 (m, 12H), 0.78 (t, J = 6.5 Hz, 6H); ^{13}C NMR ($CDCl_3$): δ 151.4, 142.9, 142.4, 139.6, 132.7, 132.4, 128.5, 128.0, 127.7, 124.0, 123.3, 121.4, 120.0, 116.2, 108.6, 55.3, 47.7, 40.8, 31.8, 30.3, 29.4, 29.4, 24.2, 22.5, 14.0; HRMS (ESI) m/z calcd for $C_{59}H_{63}N_4$ $[M+H]^+$ 827.5053, found 827.5055.

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Keywords: Intramolecular oxidative coupling • 7-Azaindoles • Fluorene based organic materials • pyrroles • Arylations

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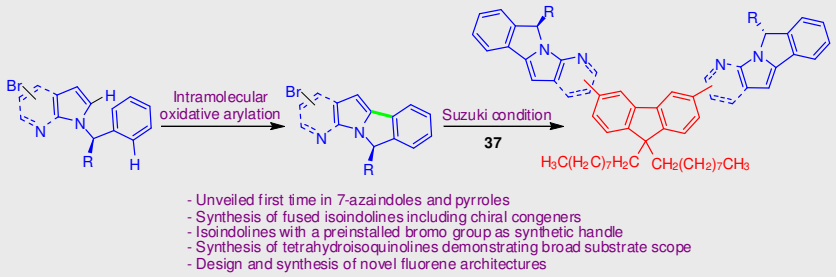

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