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One-Pot Synthesis of Imidazolyl Isoquinolines under a Palladium-Catalyzed C–H Activation/Annulation (CHAA) Reaction

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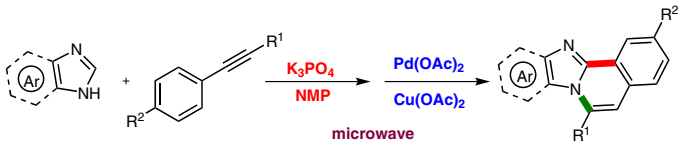

R^1 = H, aryl
R^2 = H, Me, OMe, Cl, F

11 examples
35–72%

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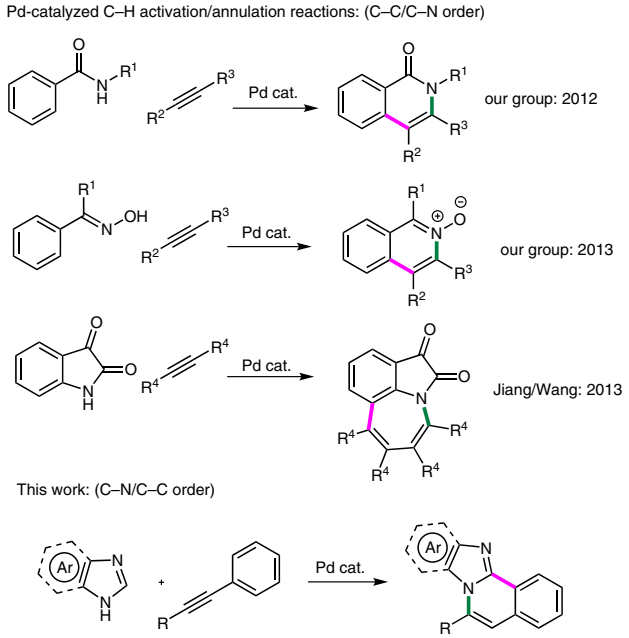
Abstract A microwave-assisted Pd-catalyzed one-pot C–H activation/annulation (CHAA) protocol has been developed for the synthesis of imidazo[2,1-*a*]isoquinolines and benzo[4,5]imidazo[2,1-*a*]isoquinolines. Further *N*-alkylation for the preparation of a series of the corresponding isoquinolium salts has also been demonstrated. The fluorescent properties of these isoquinolines have been studied.

Key words C–H activation/annulation, microwave, fluorophore, heterocycle, fluorescent

Fluorophores are a useful tool in biology for staining large molecules, such as enzymes and proteins, and they can be also used as molecular probes and indicators.[1] The search and fine tuning of glowing molecules has left challenges for chemists from a synthetic perspective. Many fluorophores have been found and discovered in the past;[2] as key fluorophores, quinoline, quinolone, isoquinoline, and isoquinolone and their salts have shown unique fluorescent properties.[3] The preparation and functionalization of these core structures by an easily accessible route has attracted reasonable attention for the discovery of new fluorophores.

Molecules having these quinolone cores have also been shown to have good biological activities against tumor cells as well as possessing DNA binding ability.[4] The construction of these heteroarene skeletons has become more convenient using recently developed C–H direct functionalization approaches using transition-metal catalysts, such as rhodium, ruthenium, palladium, and iridium.[5] We, together with other pioneers in the field, have developed ways of making these nitrogen-containing heterocycles in an atom- and step-economical fashion by using palladium catalysts. As demonstrated in Scheme 1, the construction of heteroaromatics has been realized via C–H activation/annulation reactions starting from readily available precursors. Previously we have utilized alkynes as coupling partners for the preparation of a number of heterocycles under Pd-catalyzed conditions. Under directed C–H activation processes, the new C–C bond was initially formed (marked in pink), followed by C–N bond formation (marked in green). Heterocycles, such as isoquinolone,[6] isoquinoline *N*-oxide,[7] as well as the seven-membered benzoazepine,[8] have been prepared by a single-step reaction. In this communication, we report our latest discovery on the synthesis of a new class of isoquinoline derivative via a one-pot protocol via initial C–N bond formation followed by double C–H bond activation (Scheme 1).

As proposed, the imidazo[2,1-*a*]isoquinoline ring system could be formed via hydroamination an alkyne with imidazole followed by double C–H activation of both ring systems to make the third ring. The hydroamination reaction of imidazole and a terminal alkyne was first studied. The reaction of commercially available 1*H*-imidazole (**1a**) and phenylacetylene (**2a**) in DMSO gave an 80:20 mixture of *Z*-alkene **3a** and *E*-alkene **3a′** with a full reaction conversion (Table 1, entry 1). Further screening of the reaction conditions, such as the solvent, base, and heating mode, was fruitful; inorganic bases such as K_3PO_4 and Cs_2CO_3 either in DMSO or NMP gave good *Z*/*E* selectivity (Table 1, entries 2, 3, 5, and 6). It is noteworthy that the use of base is crucial for the stereoselectivity, particularly for *Z* selectivity. This empirical observation had been previously reported in the literature, unfortunately, the mechanism is still not quite understood.[9] We envisaged that after the hydroamination of phenylacetylene, the cation–π-interaction be-



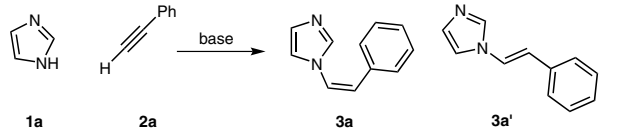
Scheme 1 C–H Activation/annulation reaction using an alkyne as the coupling partner

tween the aromatic ring and the potassium cation gives rise to the *Z*-isomer as the most stable isomer. The *Z*-alkene would be the sole isomer that could be converted into the ring system without further rotation of the C=C bond. Under conventional thermal conditions, the hydroamination reaction also went smoothly to provide the desired alkene **3a** with excellent selectivity, which agreed with results previously described in the literature.[10] When reaction was allowed to stir for 4 hours, it led to the conversion of the kinetically stable *Z*-isomer into the thermodynamically stable *E*-isomer. So the ratio of *Z*/*E* depends on the reaction time. It seemed that both DMSO and NMP were also potential solvents for the further ring-closing reaction. Solvents such as toluene, DCE, and BuOH did not provide any of the desired product **3a** or **3a′**.

With optimal conditions for the *Z*-selective hydroamination reaction in hand, we attempted to find conditions to combine both processes into a single chemical step. In the presence of base and Pd catalyst, the reaction did not give us any of the desired imidazolyl isoquinoline **4a**. With longer reaction times, *E*-alkene **3a′** was isolated as the sole product in near quantitative yield. Our focus then moved to screening the reaction conditions for an alternative one-pot reaction that combined the hydroamination and Pd-catalyzed double C–H activation as two separate steps.

As shown in Table 2, entry 4, after hydroamination in NMP, when mesitylene was used as the second solvent under Pd-catalyzed conditions in the presence of $Cu(OAc)_2$ as the oxidant, our desired imidazolyl isoquinoline **4a** was obtained in 11% yield.[11] The double C–H activation reaction is

Table 1 Screening of the Reaction Conditions for the Hydroamination of Phenylacetylene[a]

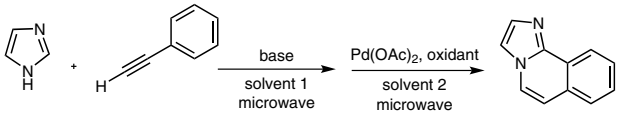


1a **2a** **3a** **3a'**

Entry	Solvent	Base	Time	Conv. (%)	Ratio[b] *Z*/*E*
1	DMSO	KOH[c]	25 min	99	80:20
2	**DMSO**	**K_3PO_4**	**25 min**	**99**	**95:5**
3	DMSO	Cs_2CO_3	25 min	99	90:10
4[d]	DMSO	K_3PO_4	24 h	99	98:2
5	**NMP**	**K_3PO_4**	**25 min**	**99**	**97:3**
6	NMP	Cs_2CO_3	25 min	99	85:15

[a] Reaction conditions: phenylacetylene (**2a**, 30.6 mg, 0.3 mmol), imidazole (**1a**, 31 mg, 0.45 mmol), solvent (1.0 mL), base (2.0 equiv), microwave conditions (120 °C, 300 W) unless otherwise stated.
[b] Ratio based on GC measurements.
[c] KOH (0.5 equiv).
[d] Under standard thermal conditions without microwave irradiation.

Table 2 Reaction Condition Screening on Double C–H Activation Ring Closure[a]



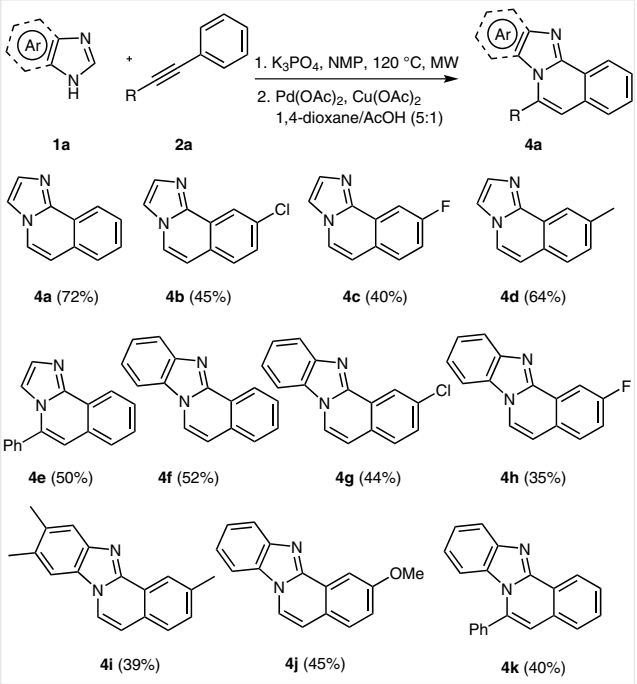
1a **2a** **4a**

Entry	Step 1		Step 2		
	Solvent 1	Base	Solvent 2	Oxidant	Yield[b] (%)
1	DMSO	Cs_2CO_3	–	AgOAc	0
2	DMSO	K_3PO_4	mesitylene	AgOAc	0
3	NMP	Cs_2CO_3	mesitylene	$Cu(OAc)_2$	<5
4	NMP	K_3PO_4	mesitylene	$Cu(OAc)_2$	11
5	NMP	K_3PO_4	1,4-dioxane	$Cu(OAc)_2$	15
6	NMP	K_3PO_4	1,4-dioxane/HOAc (10:1)	$Cu(OAc)_2$	50
7	**NMP**	**K_3PO_4**	**1,4-dioxane/HOAc (5:1)**	**$Cu(OAc)_2$**	**72**
8[c]	NMP	K_3PO_4	1,4-dioxane/HOAc (5:1)	$Cu(OAc)_2$	24
9	DMSO	K_3PO_4	1,4-dioxane/HOAc (5:1)	$Cu(OAc)_2$	52
10	NMP	Cs_2CO_3	1,4-dioxane/HOAc (5:1)	$Cu(OAc)_2$	45

[a] Reaction conditions: 1. phenylacetylene (**2a**, 30.6 mg, 0.3 mmol), imidazole (**1a**, 30.6 mg, 0.45 mmol), base (2.0 equiv), solvent 1 (1.0 mL), microwave conditions (120 °C, 300 W), 25 min; 2. $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (2.0 equiv), solvent 2 (1 mL), microwave conditions (120 °C, 300 W), 6 h, unless otherwise stated.
[b] Isolated yield.
[c] Under standard thermal conditions without microwave irradiation. Reaction time (step 1: 24 h; step 2: 48 h).

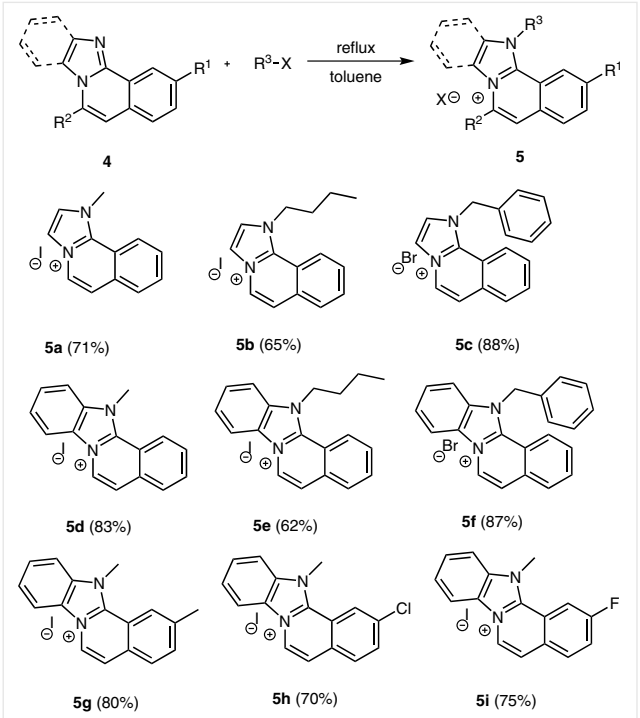
favored under acid conditions (Table 2, entry 6), the addition of acetic acid as the co-solvent provide the desired product in 50% yield over two steps and no work-up or purification was needed in between. Increasing the amount of acid led to the desired product **4a** in 72% overall yield. In contrast, under conventional thermal conditions, the desired product was obtained in 24% yield. Comparing to the reaction under microwave conditions, the reaction under thermal conditions was slower and *E*-alkene was formed from *Z*-alkene during C–H activation processes (Table 2, entry 8).

With the optimal conditions in hand, we examined the scope and limitations of this reaction (Scheme 2). To our delight, a range of imidazolyl isoquinolines **4a–e** and benzoimidazolyl isoquinolines **4f–k** were synthesized. When 1*H*-imidazole (**1a**) and terminal arylacetylenes **2** were utilized, arylacetylenes **2** bearing electron-rich or electron-deficient substituents at the *para*-position were converted into the corresponding 9-substituted imidazolyl isoquinolines **4b–d** in 40–64% yields. As this synthesis begins from cheap and readily available substrates, the efficiency of the molecular growth is very promising. An internal alkyne was also tolerated and isoquinoline **4e** was successfully prepared in 50% yield from diphenylacetylene. A range of benzoimidazolyl isoquinolines **4f–k** were prepared from 1*H*-benzimidazole (**1b**) and 5,6-dimethyl-1*H*-benzimidazole (**1c**) and aryl- and diarylacetylenes **2** under identical conditions.



Scheme 2 Microwave-assisted one-pot reaction for the synthesis of imidazolyl and benzoimidazolyl isoquinolines. *Reagents and conditions*: 1. aryl- or diarylacetylene **2** (0.3 mmol), 1*H*-imidazole (**1a**) or 1*H*-benzimidazole (**1b**) (0.45 mmol), K_3PO_4 (2.0 equiv), NMP (1.0 mL), microwave conditions (120 °C, 300 W), 10–120 min; 2. $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (2.0 equiv), 1,4-dioxane/HOAc (5:1, 1.0 mL), microwave conditions (120 °C, 300 W), 5–9 h.

The direct alkylation of imidazolyl isoquinoline derivatives **4** is straightforward; the corresponding isoquinolium salts **5** were prepared in good yields. As demonstrated in Scheme 3, the alkylation of imidazolyl isoquinoline **4a** with MeI, BuI, or BnBr gave the corresponding isoquinolium salts **5a–c** in good yields. Similar reactivity was also observed on benzoimidazolyl derivatives. The reactions with substituted imidazolyl isoquinolines with alkyl halide also gave the desired products **5g–i** in good yields.



Scheme 3 Synthesis of imidazolyl and benzoimidazolyl isoquinolium salts. *Reagents and conditions*: imidazolyl and benzoimidazolyl isoquinoline **4** (0.2 mmol), RX (2–4 mmol), toluene (0.2 M), 24 h.

The fluorescent properties of these imidazolyl isoquinolines **4** and the corresponding isoquinolium salts **5** are given in the Supporting Information and selected examples are illustrated in Table 3. As shown in the Supporting Information, most of the isoquinolium salts **5** are fluorescent with a wavelength of maximum absorbance between 253–313 nm, while emission intensities range from 347–410 nm, they have relative large Stokes shifts[12] from 88–147 nm; they show a useful to good quantum yield generally of about 40%. In particular, as compared in Table 3, benzoimidazolyl isoquinoline **4f** and its 12-methyl isoquinolium salt **5d** show stronger fluorescence than the corresponding imidazolyl derivatives **4a** and its 1-methyl salt **5a** due to the extended aromatic system with more delocalization possi-

bilities. The *para*-chloro substituent on the acetylene affected the fluorescence, as 2-chloro product **4g** had a low quantum yield (13%) compared to the unsubstituted isoquinoline **4f**. While as the quantum efficiency of the electron-donating group containing 2-methoxy product **4j** is almost the same as **4f**. It is worth noting that the 12-benzyl-substituted benzoimidazolyl isoquinolium salt **5f** gave a relative high quantum yield of 57%. In order to further increase the quantum efficiency, the future direction would be the late-stage functional group introduction via *ortho*-C–H activation protocols as well as the *meta*-selective C–H activations developed within our group[13] or the Ackermann and Frost groups.[14]

Table 3 Fluorescent Properties of Imidazolyl Isoquinoline and Isoquinolium Salts

Compound	λ_{abs} (nm)[a]	λ_{em} (nm)[a]	Stokes shift (nm)	ϕ[b] (%)
4a	254	377	123	9
4f	277	378	101	43
4g	279	378	99	13
4i	277	385	108	50
4j	281	390	109	38
5a	249	347	98	33
5d	262	409	147	43
5f	269	378	109	57

[a] Wavelengths of maximum absorbance (λ_{abs}) or emission intensity (λ_{em}).
[b] Quantum yield determined by using Rhodamine B as a standard (ϕ = 0.71).

In conclusion, we have reported a novel approach for the synthesis of a series of imidazolyl isoquinoline and the corresponding isoquinolium salts via a one-pot Pd-catalyzed CHAA reaction. The preliminary fluorescent property studies have provided potentially good fluorophores for future investigations of structure–function relationships.

Flash chromatography was performed on silica gel 100–200 μm. The solvent system used was a gradient of petroleum ether/EtOAc, increasing in polarity to EtOAc. TLC was performed on glass backed plates pre-coated with silica (GF254), which were developed using standard visualizing agents. ^{1}H and ^{13}C NMR spectra were recorded on a 600 MHz or 400 MHz Bruker Avance spectrometer at 25 °C with the solvent resonance as the internal standard (^{1}H: $CHCl_3$: δ = 7.26; DMSO: δ = 2.50).^{13}C NMR spectra were recorded with complete proton decoupling with the solvent resonance as the internal standard. LR-MS were recorded on Micromass Autospec, operating in Agilent GC-MS operating in either EI or CI mode. HRMS recorded for accurate mass analysis, were performed on either a Q-TOF micro (Bruker Compass Data Analysis 4.0) spectrometer. The UV-vis and fluorescence spectra were performed on Hitachi (U-3900) and Edinburgh (FLS 980).

Reagents and solvents were commercially available and were used without further purification. Phenylacetylene and imidazole were purchased from Heowns. Diarylacetylenes were prepared via Sonogashira coupling reactions of the corresponding arylacetylene and iodoarene using the literature procedures. The analytical data of products are in agreement with previously reported data.

Imidazo[2,1-*a*]isoquinolines 4a–k; General Procedure

Into a 10-mL microwave vial was weighed arylacetylene (0.3 mmol), imidazole (2.0 equiv), and K_3PO_4 (2.0 equiv). The vial was charged with a magnetic stir bar and subsequently NMP (1.0 mL) was added as the solvent. The microwave vial cap was affixed onto the vial and the mixture was heated in the microwave at 120 °C (300 W) for 10–120 min (t_1). After the first step was complete, without purification, to the mixture was added $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (2 equiv), HOAc (200 μL), and dioxane (1.0 mL). Then the mixture was heated at 120 °C (300 W) in the microwave for 5–9 h (t_2). The reaction course was monitored by GC-MS or TLC. The vessel was cooled to r.t., the mixture was diluted with EtOAc (20 mL), and it was transferred to a separatory funnel, and washed with water (3 × 30 mL) and brine (45 mL). The organic phase was dried (Na_2SO_4) and filtered and the solvent was removed under reduced pressure to provide the crude product. The purification was performed by flash column chromatography (silica gel).

Imidazo[2,1-*a*]isoquinoline (4a)

t_1 = 25 min; t_2 = 6 h. Yellow solid; yield: 36 mg (72%); mp 69–70 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.63 (d, *J* = 8.0 Hz, 1 H), 7.91 (d, *J* = 7.0 Hz, 1 H), 7.69 (d, *J* = 8.0 Hz, 1 H), 7.67–7.53 (m, 4 H), 7.03 (d, *J* = 7.0 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.2, 131.4, 129.4, 128.2, 128.2, 126.9, 124.0, 123.2, 123.1, 114.2, 113.2.

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{11}H_8N_2$: 168.0687; found: 168.0688.

9-Chloroimidazo[2,1-*a*]isoquinoline (4b)

t_1 = 10 min; t_2 = 6 h. Yellow solid; yield: 27 mg (45%); mp 70–72 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.60 (d, *J* = 2.0 Hz, 1 H), 7.89 (d, *J* = 7.0 Hz, 1 H), 7.60 (m, 3 H), 7.49 (dd, *J* = 9.0, 2.0 Hz, 1 H), 7.00 (d, *J* = 7.5 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.0, 134.1, 131.8, 128.6, 128.4, 127.6, 125.0, 123.3, 122.8, 114.6, 112.5.

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{11}H_7{}^{35}ClN_2$: 202.0298; found: 202.0299.

9-Fluoroimidazo[2,1-*a*]isoquinoline (4c)

t_1 = 10 min; t_2 = 6 h. Yellow solid; yield: 22 mg (40%); mp 65–66 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27 (dd, *J* = 9.5, 2.5 Hz, 1 H), 7.90 (d, *J* = 7.5 Hz, 1 H), 7.70 (dd, *J* = 9.0, 5.5 Hz, 1 H), 7.62 (s, 1 H), 7.59 (s, 1 H), 7.30 (td, *J* = 9.0, 2.5 Hz, 1 H), 7.04 (d, *J* = 7.5 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.3 (d, *J* = 248.5 Hz), 131.7, 129.3 (d, *J* = 8.8 Hz), 125.9 (d, *J* = 2.1 Hz), 125.5, 122.4 (d, *J* = 2.1 Hz), 116.9 (d, *J* = 24.0 Hz), 114.6, 112.6, 110.8, 108.6 (d, *J* = 23.8 Hz).

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{11}H_7{}^{19}FN_2$: 186.0593; found: 186.0597.

9-Methylimidazo[2,1-*a*]isoquinoline (4d)

t_1 = 30 min; t_2 = 6 h. Yellow solid; yield: 35 mg (64%); mp 78–79 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.45 (s, 1 H), 7.86 (d, *J* = 7.5 Hz, 1 H), 7.55–7.61 (m, 3 H), 7.39 (d, *J* = 8.0 Hz, 1 H), 7.02 (d, *J* = 7.5 Hz, 1 H), 2.56 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.4, 131.3, 129.7, 129.4, 127.2, 126.8, 124.0, 123.0, 122.3, 114.2, 113.0, 21.8.

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{12}H_{10}N_2$: 182.0844; found: 182.0846.

5-Phenylimidazo[2,1-*a*]isoquinoline (4e)

t_1 = 120 min; t_2 = 9 h. Yellow solid; yield: 36 mg (50%); mp 120–122 °C.

IR (KBr): 3552, 2989, 2413, 1720, 1617, 1449, 1324, 766 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.67 (d, *J* = 5.5 Hz, 1 H), 7.72 (d, *J* = 5.5 Hz, 1 H), 7.67–7.63 (m, 3 H), 7.61–7.50 (m, 6 H), 7.02 (s, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 143.7, 135.9, 134.4, 131.0, 129.9, 129.7, 129.1, 128.6, 128.4, 128.0, 126.9, 123.3, 123.1, 113.1, 99.9.

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{17}H_{12}N_2$: 244.1000; found: 244.1000.

Benzo[4,5]imidazo[2,1-*a*]isoquinoline (4f)

t_1 = 25 min; t_2 = 6 h. Yellow solid; yield: 34 mg (52%); mp 111–112 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.83 (m, 1 H), 8.16 (d, *J* = 8.0 Hz, 1 H), 8.02 (d, *J* = 8.5 Hz, 1 H), 7.83 (d, *J* = 8.0 Hz, 1 H), 7.74 (m, 1 H), 7.68 (m, 2 H), 7.52 (td, *J* = 7.5, 1.0 Hz, 1 H), 7.42 (td, *J* = 8.0, 1.0 Hz, 1 H), 7.07 (d, *J* = 7.0 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 146.3, 142.8, 130.6, 129.1, 129.0, 127.2, 126.0, 124.0, 123.7, 122.6, 120.8, 120.4, 118.9, 110.3, 108.8.

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{15}H_{10}N_2$: 218.0844; found: 218.0842.

2-Chlorobenzo[4,5]imidazo[2,1-*a*]isoquinoline (4g)

t_1 = 10 min; t_2 = 6 h. Yellow solid; yield: 33 mg (44%); mp 152–155 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.74 (d, *J* = 2.0 Hz, 1 H), 8.05 (d, *J* = 7.0 Hz, 1 H), 7.99 (d, *J* = 8.0 Hz, 1 H), 7.76 (d, *J* = 8.5 Hz, 1 H), 7.59 (d, *J* = 8.5 Hz, 1 H), 7.51 (m, 2 H), 7.39 (t, *J* = 8.0 Hz, 1 H), 6.95 (d, *J* = 7.0 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.9, 143.6, 134.1, 130.3, 129.9, 129.7, 128.4, 125.0, 124.5, 124.4 122.3, 121.5, 120.0, 110.5, 109.9.

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{15}H_9{}^{35}ClN_2$: 252.0454; found: 252.0455.

2-Fluorobenzo[4,5]imidazo[2,1-*a*]isoquinoline (4h)

t_1 = 10 min; t_2 = 6 h. Brown solid; yield: 24 mg (35%); mp 172–174 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.47 (dd, *J* = 9.5, 2.5 Hz, 1 H), 8.15 (d, *J* = 7.5 Hz, 1 H), 8.02 (d, *J* = 8.5 Hz, 1 H), 7.85 (d, *J* = 8.0 Hz, 1 H), 7.75 (dd, *J* = 8.5, 5.5 Hz, 1 H), 7.53 (t, *J* = 8.0 Hz, 1 H), 7.47–7.37 (m, 2 H), 7.07 (d, *J* = 7.5 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.2 (d, *J* = 249.0 Hz), 143.6 (s), 129.4 (d, *J* = 8.5 Hz), 128.1, 128.1, 125.1 (d, *J* = 9.5 Hz), 125.0, 122.3, 120.7 (d, *J* = 2.5 Hz), 120.0, 118.7 (d, *J* = 24.0 Hz), 110.8, 110.8, 110.5 (d, *J* = 24.0 Hz), 110.0.

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{15}H_9FN_2$: 236.0750; found: 236.0751.

2,9,10-Trimethylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (4i)

t_1 = 25 min; t_2 = 6 h. Yellow solid; yield: 30.5 mg (39%); mp 197–199 °C.

IR (KBr): 3020, 2920, 2853, 1732, 1518, 1458, 1363, 1003, 824 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.59 (s, 1 H), 8.00 (d, *J* = 7.0 Hz, 1 H), 7.74 (s, 1 H), 7.60 (d, *J* = 8.0 Hz, 1 H), 7.53 (s, 1 H), 7.45 (d, *J* = 8.0 Hz, 1 H), 6.96 (d, *J* = 7.5 Hz, 1 H), 2.57 (s, 3 H), 2.45 (s, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 146.7, 142.4, 138.3, 133.7, 131.1, 129.1, 128.6, 126.9, 124.5, 123.7, 120.6, 119.7, 110.8, 109.9, 21.6, 20.70, 20.68.

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{18}H_{16}N_2$: 260.1313; found: 260.1314.

2-Methoxybenzo[4,5]imidazo[2,1-*a*]isoquinoline (4j)

t_1 = 40 min; t_2 = 6 h. White solid; yield: 33 mg (45%); mp 124–125 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 2.5 Hz, 1 H), 8.09 (d, *J* = 7.5 Hz, 1 H), 8.03 (d, *J* = 8.0 Hz 1 H), 7.84 (d, *J* = 8.0 Hz, 1 H), 7.67 (d, *J* = 8.5 Hz, 1 H), 7.52 (td, *J* = 8.0, 1.5 Hz, 1 H), 7.41 (td, *J* = 8.0, 1.5 Hz, 1 H), 7.28 (dd, *J* = 9.0, 3.0 Hz, 1 H), 7.04 (d, *J* = 7.5 Hz, 1 H), 4.04 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.7, 147.2, 143.8, 130.2, 128.7, 125.7, 124.9, 124.7, 121.8, 120.8, 119.8, 119.2, 111.2, 110.0, 105.1, 55.9.

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{16}H_{12}N_2O$: 248.0950; found: 248.0953.

6-Phenylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (4k)

t_1 = 120 min; t_2 = 9 h. Yellow solid; yield: 35 mg (40%); mp 171–173 °C.

IR (KBr): 3552, 3235, 2027, 1617, 1527, 1394, 1311, 1274, 878 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.89 (m, 1 H), 7.99 (d, *J* = 8.0 Hz, 1 H), 7.77–7.54 (m, 8 H), 7.40 (td, *J* = 8.0, 1.0 Hz, 1 H), 7.00 (td, *J* = 8.0, 1.0 Hz, 1 H), 6.91 (s, 1 H), 6.49 (d, *J* = 9.0 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 148.3, 144.3, 137.5, 134.7, 131.6, 130.7, 130.1, 129.9, 129.4, 129.0, 127.9, 126.7, 125.1, 124.2, 122.9, 121.3, 119.7, 114.1, 112.6.

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{21}H_{14}N_2$: 294.1157; found: 294.1158.

1-Alkylimidazo[2,1-*a*]isoquinolium Salts 5a–i; General Procedure

Freshly made imidazo[2,1-*a*]isoquinoline **4** (0.2 mmol) was dissolved in toluene (1 ml) and the electrophilic agent (10–20 equiv) was added. The reaction was stirred for 24 h under reflux. The final product precipitated from the solution and it was recovered by filtration. The residue was washed extensively with Et_2O and dried to yield the corresponding 1-alkylimidazo[2,1-*a*]isoquinolium salt framework **5a–i**.

1-Methyl-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium Iodide (5a)

White solid; yield: 44 mg (71%); mp 251–254 °C.

IR (KBr): 3549, 3236, 2024, 1618, 1548, 1483, 1455, 803, 746 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.79 (d, *J* = 8.0 Hz, 1 H), 8.67 (d, *J* = 7.5 Hz, 1 H), 8.45 (d, *J* = 2.0 Hz, 1 H), 8.26 (d, *J* = 2.0 Hz, 1 H), 8.24 (d, *J* = 8.0 Hz, 1 H), 8.00 (m, 2 H), 7.90 (d, *J* = 7.2 Hz, 1 H), 4.48 (s, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 136.9, 132.4, 132.2, 130.2, 129.0, 127.5, 125.1, 124.8, 118.4, 117.9, 116.5, 39.1.

HRMS (ESI): *m*/*z* $[M - I]^+$ calcd for $C_{12}H_{11}IN_2$: 183.0922; found: 183.0924.

1-Butyl-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium Iodide (5b)

Yellow solid; yield: 46 mg (65%); mp 138–141 °C.

IR (KBr): 3550, 3065, 2953, 1726, 1545, 1521, 1214, 1070, 815 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.67 (d, J = 7.0 Hz, 1 H), 8.64 (dd, J = 7.5, 2.0 Hz, 1 H), 8.49 (d, J = 2.0 Hz, 1 H), 8.31 (d, J = 2.0 Hz, 1 H), 8.27–8.22 (m, 1 H), 8.06–7.96 (m, 2 H), 7.91 (d, J = 7.5 Hz, 1 H), 4.87 (t, J = 7.5 Hz, 2 H), 2.04–1.85 (m, 2 H), 1.46 (m, 2 H), 0.95 (t, J = 7.5 Hz, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 136.2, 132.7, 132.2, 130.5, 129.3, 126.8, 125.3, 124.4, 118.1, 117.9, 116.93, 50.60, 31.11, 19.47, 14.01.

HRMS (ESI): m/z [M – I]$^+$ calcd for $C_{15}H_{17}IN_2$: 225.1392; found: 225.1392.

1-Benzyl-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium Bromide (5c)

White solid; yield: 68 mg (88%); mp 245–247 °C.

IR (KBr): 3551, 3148, 3065, 1617, 1546, 1463, 1359, 1181, 806 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.78 (d, J = 7.5 Hz, 1 H), 8.63 (s, 1 H), 8.43 (d, J = 8.5 Hz, 1 H), 8.38 (s, 1 H), 8.22 (d, J = 8.0 Hz, 1 H), 7.95 (m, 2 H), 7.81 (t, J = 8.0 Hz, 1 H), 7.40 (t, J = 7.5 Hz, 2 H), 7.34 (t, J = 7.5 Hz, 1 H), 7.29 (d, J = 7.5 Hz, 2 H), 6.22 (s, 2 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 136.3, 134.2, 132.3, 131.9, 129.7, 129.1, 128.6, 128.2, 126.8, 126.4, 125.0, 124.0, 117.9, 117.1, 117.0, 53.1.

HRMS (ESI): m/z [M – Br]$^+$ calcd for $C_{18}H_{15}{}^{79}BrN_2$: 259.1235; found: 259.1236.

12-Methyl-12*H*-benzo[4,5]imidazo[2,1-*a*]isoquinolin-7-ium Iodide (5d)

White solid; yield: 60 mg (83%); mp 280–283 °C.

IR (KBr): 3549, 3018, 1617, 1528, 1478, 1419, 1252, 1001, 755 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.34 (d, J = 7.5 Hz, 1 H), 9.10 (d, J = 8.5 Hz, 1 H), 8.69 (d, J = 8.5 Hz, 1 H), 8.35 (m, 2 H), 8.16 (t, J = 8.0 Hz, 1 H), 8.11–8.02 (m, 2 H), 7.93 (t, J = 8.5 Hz, 1 H), 7.84 (t, J = 8.5 Hz, 1 H), 4.65 (s, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 141.5, 134.9, 133.9, 133.6, 130.3, 129.2, 129.0, 127.1, 126.7, 126.2, 123.3, 118.12, 117.2, 113.9, 113.4, 35.4.

HRMS (ESI): m/z [M – I]$^+$ calcd for $C_{16}H_{13}IN_2$: 233.1079; found: 233.1078.

12-Butyl-12*H*-benzo[4,5]imidazo[2,1-*a*]isoquinolin-7-ium Iodide (5e)

White solid; yield: 50 mg (62%); mp 252–254 °C.

IR (KBr): 3550, 3037, 1920, 1617, 1526, 1472, 1455, 1367, 750 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.35 (d, J = 7.5 Hz, 1 H), 8.87 (d, J = 8.5 Hz, 1 H), 8.70 (d, J = 8.5 Hz, 1 H), 8.35 (m, 2 H), 8.20–8.04 (m, 3 H), 7.92 (t, J = 7.5 Hz, 1 H), 7.84 (t, J = 8.0 Hz, 1 H), 5.16 (t, J = 7.5 Hz, 2 H), 2.01 (dt, J = 15.0, 7.5 Hz, 2 H), 1.55 (dq, J = 15.0, 7.5 Hz, 2 H), 0.95 (t, J = 7.3 Hz, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 140.6, 135.1, 133.8, 133.4, 130.8, 129.5, 129.1, 127.3, 126.3, 126.0, 123.6, 117.7, 117.3, 114.0, 113.5, 46.9, 31.1, 19.8, 14.2.

HRMS (ESI): m/z [M – I]$^+$ calcd for $C_{21}H_{19}IN_2$: 275.1548; found: 275.1550.

12-Benzyl-12*H*-benzo[4,5]imidazo[2,1-*a*]isoquinolin-7-ium Bromide (5f)

White solid; yield: 75 mg (87%); mp 253–255 °C.

IR (KBr):3550, 3413, 2995, 1617, 1525, 1472, 1327, 803, 752 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.44 (d, J = 7.5 Hz, 1 H), 8.77 (dd, J = 7.5 Hz, J = 2.0 Hz, 1 H), 8.61 (d, J = 8.5 Hz, 1 H), 8.33 (d, J = 8.0 Hz, 1 H), 8.27 (dd, J = 8.0 Hz, J = 2.0 Hz, 1 H), 8.16 (d, J = 7.5 Hz, 1 H), 8.08 (t, J = 8.0 Hz, 1 H), 7.93–7.83 (m, 3 H), 7.44–7.30 (m, 5 H), 6.48 (s, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 141.4, 135.3, 134.6, 134.0, 133.8, 130.4, 129.6, 129.4, 129.3, 128.6, 127.6, 126.6, 126.5, 125.9, 123.8, 117.6, 117.3, 114.2, 113.3, 50.2.

HRMS (ESI): m/z [M – Br]$^+$ calcd for $C_{22}H_{17}{}^{79}BrN_2$: 309.1386; found: 309.1387.

2,12-Dimethyl-12*H*-benzo[4,5]imidazo[2,1-*a*]isoquinolin-7-ium Iodide (5g)

White solid; yield: 59 mg (80%); mp 287–290 °C.

IR (KBr): 3550, 3413, 3019, 1619, 1532, 1500, 1448, 1035, 770 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.27 (d, J = 7.5 Hz, 1 H), 8.84 (s, 1 H), 8.67 (d, J = 8.5 Hz, 1 H), 8.35 (d, J = 8.5 Hz, 1 H), 8.22 (d, J = 8.5 Hz, 1 H), 8.03 (d, J = 7.0 Hz, 1 H), 7.98 (d, J = 8.0 Hz, 1 H), 7.91 (t, J = 7.5 Hz, 1 H), 7.82 (t, J = 7.5 Hz, 1 H), 4.66 (s, 3 H), 2.71 (s, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 141.2, 140.7, 135.4, 133.6, 132.8, 129.0, 128.9, 127.1, 126.1, 125.6, 122.5, 118.2, 117.1, 113.9, 113.4, 35.5, 22.0.

HRMS (ESI): m/z [M – I]$^+$ calcd for $C_{17}H_{15}IN_2$: 247.1235; found: 247.1235.

2-Chloro-12-methyl-12*H*-benzo[4,5]imidazo[2,1-*a*]isoquinolin-7-ium Iodide (5h)

White solid; yield: 55 mg (70%); mp 238–241 °C.

IR (KBr): 3529, 3030, 1950, 1534, 1446, 1413, 1318, 879, 764 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.38 (d, J = 6.5 Hz, 1 H), 9.00 (s, 1 H), 8.70 (d, J = 8.0 Hz, 1 H), 8.38 (t, J = 8.0 Hz, 2 H), 8.22 (d, J = 8.0 Hz, 1 H), 8.12 (d, J = 6.0 Hz, 1 H), 7.94 (t, J = 7.0 Hz, 1 H), 7.87 (t, J = 7.0 Hz, 1 H), 4.68 (s, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 140.5, 134.9, 134.1, 133.6, 133.5, 131.2, 129.3, 127.0, 126.5, 125.5, 123.9, 119.3, 116.7, 114.0, 113.6, 35.2.

HRMS (ESI): m/z [M – I]$^+$ calcd for $C_{16}H_{12}{}^{35}ClIN_2$: 267.0689; found: 267.0688.

2-Fluoro-12-methyl-12*H*-benzo[4,5]imidazo[2,1-*a*]isoquinolin-7-ium Iodide (5i)

Yellow solid; yield: 56 mg (75%); mp 255–259 °C.

IR (KBr): 3013, 1648, 1620, 1503, 1412, 1287, 1213, 1036, 714 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.35 (d, J = 7.5 Hz, 1 H), 8.84 (dd, J = 10.5, 2.5 Hz, 1 H), 8.70 (d, J = 8.0 Hz, 1 H), 8.44 (dd, J = 9.0, 6.0 Hz, 1 H), 8.38 (d, J = 8.5 Hz, 1 H), 8.16–8.06 (m, 2 H), 7.94 (t, J = 8.0 Hz, 1 H), 7.85 (t, J = 7.5 Hz, 1 H), 4.66 (s, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 162.1 (d, J = 248.5 Hz), 140.8 (d, J = 4.5 Hz), 133.6, 132.2 (d, J = 9.5 Hz), 131.8, 129.2, 127.0, 126.4, 122.96 (d, J = 23.7 Hz), 122.92 (d, J = 2.5 Hz), 119.3 (d, J = 10.5 Hz), 116.7, 114.0, 113.5, 112.1 (d, J = 26.0 Hz), 35.1.

HRMS (ESI): m/z [M – I]$^+$ calcd for $C_{16}H_{12}FIN_2$: 251.0985; found: 251.0986.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588101.

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