Effective Suzuki–Miyaura Arylation and Sonogashira Aryl Alkynylation on N-Heteroaromatic Cations: Synthesis of Substituted Pyridine-Fused Cationic Heterocycles

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Abstract: Suzuki–Miyaura and Sonogashira cross-coupling reactions were efficiently employed for the syntheses of aryl, biaryl, and aryl alkynyl substituted polycyclic tetrahydropyrimidinium, diazepanium, and diazocanium derivatives with moderate-to-high yields. Appropriately functionalized pyridinium templates for these syntheses were obtained under microwave irradiation, using basic alumina as the solid support.

Key words: Suzuki–Miyaura, Sonogashira, cross-coupling, fused rings, diazepanium, diazocanium

Promising bioactivities of various heterocyclic ammonium salts,[1] for example, CFTR activation,[2] DNA-intercalation,[3] antiproliferative activity,[3] antimalarial and antileishmanial activity,[4] have attracted the attention of biologists as well as organic chemists in the last decade. Thus, the syntheses of novel entities having heteroaromatic cations at their core and derivatization of these species by introducing different functionalities to modulate the potentiality of such bioactive systems has become a popular area of research in recent times. Among the tools available for derivatization, the application of palladium-mediated cross-couplings has been very popular.[5] Because the aryl and biaryl motifs are found in a wide range of pharmaceuticals, herbicides and natural products, with or without heteroaromatic cations in their core,[5c,6] the well-known Suzuki–Miyaura cross-coupling reaction of aryl halides with aryl boronic acids has emerged as one of the most versatile and widely employed reactions for the selective derivatization of novel heteroaromatics into their aryl/biaryl analogues.[7] In recent years, aryl alkynyl substituted heterocycles have also gained immense importance. Apart from the biological importance of alkynyl heteroaromatics,[8] the presence of aryl alkynyl moieties directly linked to heteroaromatic cations (Figure 1) are well known to produce cationic π-electron systems with high quadratic hyperpolarizability, leading to the chromophores having optimized second-order nonlinear-optical (NLO) properties.[5b] Thus, the incorporation of alkynyl moieties into a heteroaromatic cationic core, through the widely used Sonogashira reaction,[9] has received substantial attention of late.[5a,e]

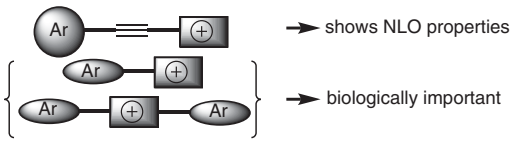
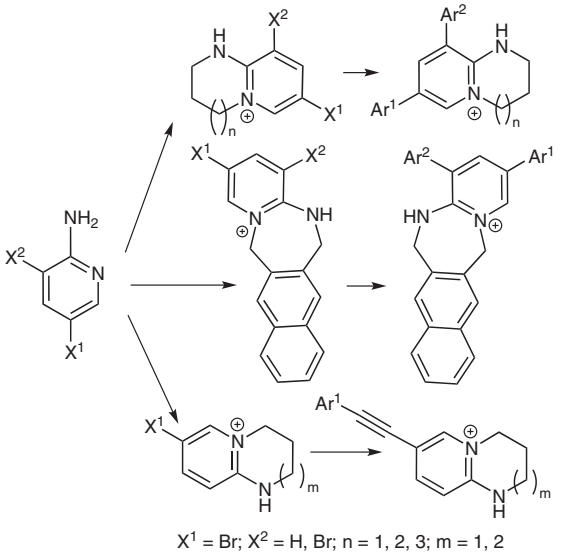


Figure 1 Importance of aryl/biaryl/aryl alkynyl substituted heteroaromatic cations

For several years we have been engaged in the synthesis of structurally unique polynuclear N-heteroaromatics and, as a part of that effort, have very recently reported the synthesis of a range of substituted oxaza-heterocycle-fused polynuclear heteroaromatics, by employing Suzuki–Miyaura and Sonogashira cross-coupling reactions.[10] In a continuation of our studies on the synthesis of novel classes of aryl/biaryl/aryl alkynyl substituted N-heteroaromatics, we decided to apply the aforesaid versatile cross-coupling techniques on the pyridine-fused diaza-heterocycles for the construction of diversely substituted tetrahydropyrimidiniums, diazepaniums, and diazocaniums from readily available starting materials (Scheme 1).



X^1 = Br; X^2 = H, Br; n = 1, 2, 3; m = 1, 2

Scheme 1 Aryl/biaryl/aryl alkynyl derivatization of fused pyridiniums

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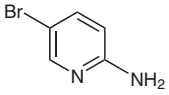
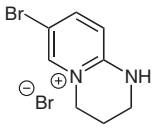
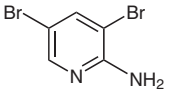
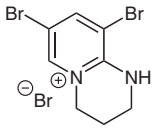
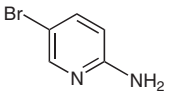
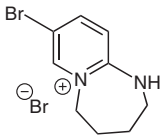
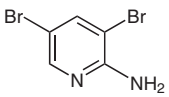
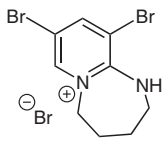
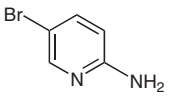
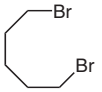
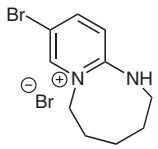
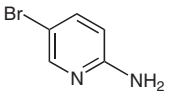
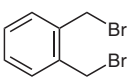
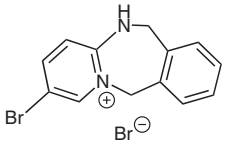
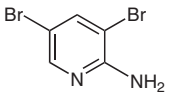
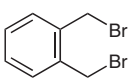
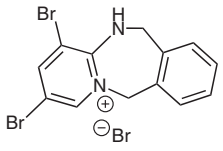
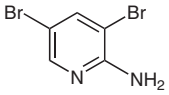
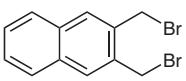
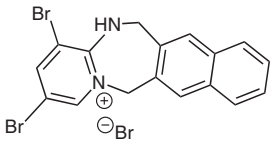
In this paper, we wish to report for the first time a simple and efficient protocol for the synthesis of aryl, biaryl and aryl alkynyl analogues of pyridine fused polycyclic tetrahydropyrimidiniums, diazepaniums, and diazocaniums, using Suzuki–Miyaura and Sonogashira cross-coupling reactions.

To construct the substrates for Suzuki–Miyaura and Sonogashira derivatization, the halogen-substituted 2-aminopyridines **1a** and **1b** were condensed with aliphatic/benzylic dibromides **2a–e**. For this, we employed our recently reported basic-alumina-supported methodology

Table 1 Construction of Pyrido-Fused Tetrahydropyrimidiniums, Diazepaniums, and Diazacaniums **3a–h** from Pyridine-2-amines under Optimal Conditions[a]

Entry	Pyridine derivative	Dibromide	Product	Time (min)	Yield (%)[b]
1	 **1a**	 **2a**	 **3a**	5	87
2	 **1b**	 **2a**	 **3b**	6	82
3	 **1a**	 **2b**	 **3c**	7	85
4	 **1b**	 **2b**	 **3d**	5	87
5	 **1a**	 **2c**	 **3e**	12	73
6	 **1a**	 **2d**	 **3f**	5	89
7	 **1b**	 **2d**	 **3g**	5	78
8	 **1b**	 **2e**	 **3h**	10	73

[a] All the reactions were performed using basic alumina as solid support under microwave irradiation at 180 W.
[b] Isolated yield.

under microwave irradiation.[11] All the templates were prepared by this procedure in high yield (Table 1).

We next focused our attention on the derivatization of these templates into their aryl and biaryl analogues, through the well-known Suzuki–Miyaura arylation technique. However, the basic-alumina-supported reaction protocol[10a] and Amberlite IRA 402 (OH) resin catalyzed conditions,[10c] reported by us recently, proved to be ineffective in this case. These conditions either failed to initiate the reaction or produced an inseparable mixture of compounds through the decomposition of staring materials (Table 2, entries 1 and 2). Neither did we find any report in the literature for the arylation of a fused polycyclic pyridinium without conversion into a pyridone.[12] Given the importance of ensuring complete absence of air and water from the reaction medium, the model reaction partners 7-bromo-1,2,3,4-tetrahydro-pyrido[1,2-*a*]pyrimidin-5-ylium bromide (**3a**) and 2-methoxybenzene boronic acid (**4a**) were reacted in anhydrous solvent under an inert atmosphere in a microwave reactor.

Table 2 Optimization of Reaction Conditions between **3a** and **4a** Catalyzed by $[Pd(PPh_3)_4]$ under Microwave Irradiation[a]

Entry	Solvent	Base	Time (min)	Temp (°C)	Yield (%)[b]
1	H_2O	resin[10c]	10 h	90	0[c]
2	–	alumina[10a]	10	120	NR[d]
3	DMSO	K_2CO_3	10	85	10
4	DMSO	Na_2CO_3	10	85	19
5	DMF	Na_2CO_3	2	80	46
6	DMF	Na_2CO_3	4	80	81
7	DMF	Na_2CO_3[e]	5	85	0[c]
8	DMF	Na_2CO_3	20	85	0[c]

[a] All the reactions were performed at 180 W, using base (1 equiv).
[b] Isolated yield.
[c] Inseparable mixture of compounds.
[d] NR = No reaction.
[e] 10 equiv base was used.

A systematic study was carried out by varying the solvent, base, catalyst, and the reaction parameters. Initially, when the test reactants **3a** and **4a** were irradiated at 85 °C for 10 minutes in dimethyl sulfoxide (DMSO), using K_2CO_3 as the base, the product **5a** was isolated in only 10% yield (Table 2, entry 3). Replacement of K_2CO_3 by Na_2CO_3 improved the yield marginally (Table 2, entry 4). Using DMF instead of DMSO as the solvent and reducing the reaction time improved the yield to 46% (Table 2, entry 5). However, the yield was maximized when the reaction partners **3a** (3 mmol) and **4a** (3.3 mmol), $[Pd(PPh_3)_4]$ (0.1 mmol) and Na_2CO_3 (1 equiv) were irradiated in a microwave reactor at 80 °C (100 W) for four minutes; these conditions produced the aryl-substituted tetrahydropyridopyrimidinium **5a** with 81% yield (Table 2, entry 6) without any trace of the corresponding pyridone. However, use of a larger amount of base (Table 2, entry 7) or longer exposure time (Table 2, entry 8) led to the formation of an inseparable mixture of compounds.

Replacement of **4a** by its isomer **4b** gave the corresponding arylated pyridinium **5b** with a marginal increase in the overall yield (84%), probably due to the decreased steric interaction in **5b** (Table 3, entry 2). A similar reaction with naphthalene-2-boronic acid (**4c**) produced 7-naphthalen-2-yl-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrimidin-5-ylium bromide (**5c**), with 78% yield (Table 3, entry 3).

To synthesize the biarylated analogue, the starting material **3a** was replaced with **3b** and the biarylation was carried out with *p*-chlorobenzene boronic acid (**4d**), leading to the formation of 7,9-bis(4-chlorophenyl)-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrimidin-5-ylium bromide (**5d**), with high yield (Table 3, entry 4).

After the successful transformation of the six-membered diaza ring systems into their aryl/biaryl analogues, we moved towards the diazepanium series. When the diazepaniums **3c**, **3d**, and **3h** were subjected to Suzuki–Miyaura derivatization with **4c**, **4d**, and **4b**, respectively, the arylated (**5e**) and biarylated (**5f** and **5g**) diazepaniums were isolated in high yields (Table 3, entries 5–7). Similarly, the arylated diazocanium **5h** was obtained from the corresponding diazocanium **3e**, under identical reaction conditions (Table 3, entry 8). We then carried out the aryl alkynylation of the pyridinium compounds using the well-known Sonogashira cross-coupling reaction. Thus, when 7-bromo-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrimidin-5-ylium bromide (**3a**) was reacted with phenyl acetylene (**6a**), the corresponding aryl-alkynyl pyridinium **7a** was obtained in 76% yield (Table 3, entry 9). A slight decrease in the yield (Table 3, entry 10) of the alkynylated product was observed when **6a** was replaced by *p*-fluorophenylacetylene (**6b**), probably due to a lowering of activity of the copper-acetylide by the fluoride-substituent. Similar results were also observed when **3a** was replaced by **3b** and the cross-coupling was carried out with **6a** and **6b**, respectively, leading to the formation of 8-phenylethynyl-2,3,4,5-tetrahydro-1*H*-pyrido[1,2-*a*][1,3]diazepin-6-ylium bromide (**7c**) and 8-(4-fluorophenylethynyl)-2,3,4,5-tetrahydro-1*H*-pyrido[1,2-*a*][1,3]diazepin-6-ylium bromide (**7d**) with moderate yields (Table 3, entries 11 and 12). All the products were characterized by NMR and mass spectroscopic analyses.

Thus, a complete and selective construction of aryl/biaryl/aryl alkynyl substituted six- to eight-membered diaza-heterocycle-fused pyridinium salts has been achieved, without disturbing the stability of the pyridinium core. Regarding the mechanistic course, it is expected that both the Suzuki–Miyaura and Sonogashira reactions proceeds through the usual oxidative addition and reductive elimination pathway on the palladium center (Scheme 2).

Table 3 Construction of Arylated/Biarylated/Aryl Alkynylated Pyrido-Fused Tetrahydropyrimidiniums, Diazepaniums, and Diazacaniums **5a–h** and **7a–d**

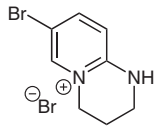
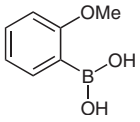
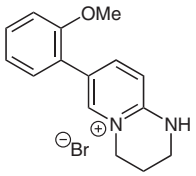
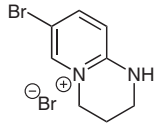
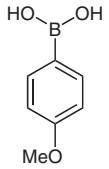
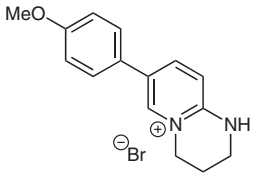
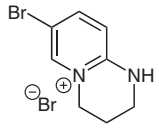
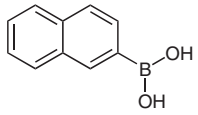
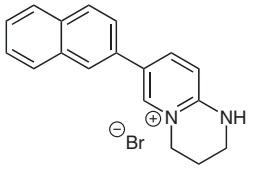
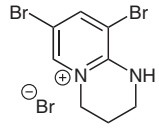
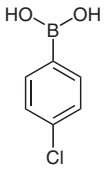
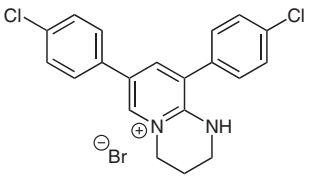
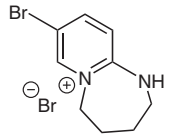
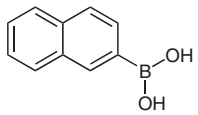
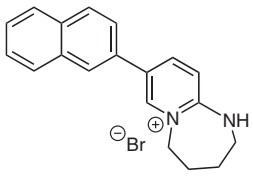
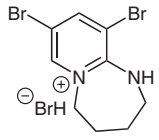
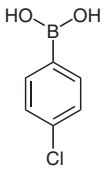
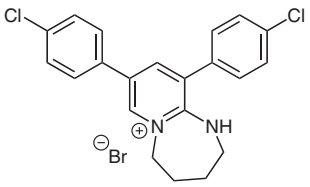
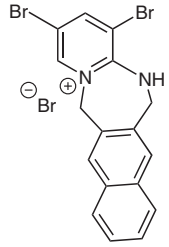
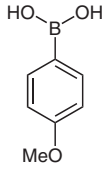
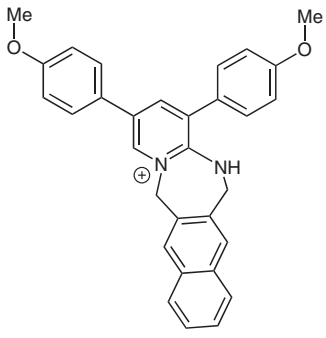
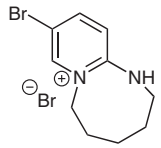
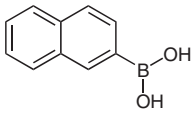
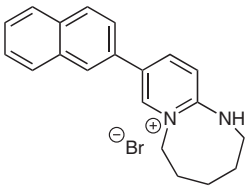
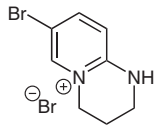
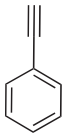
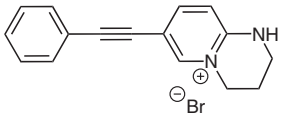
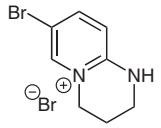
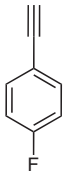
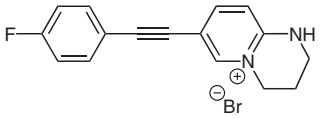
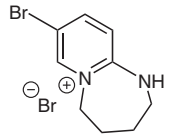
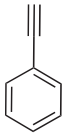
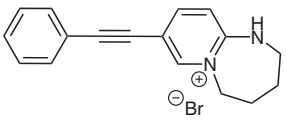
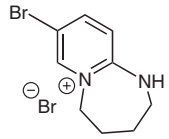
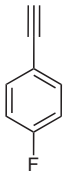
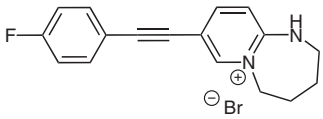
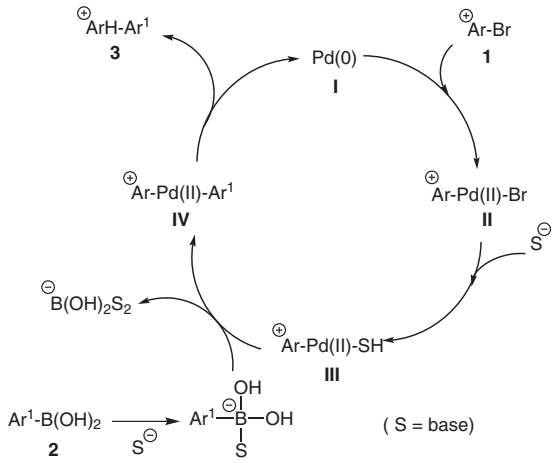
Entry	Pyridinium derivative	Boronic acid	Product[a]	Time (min)	Yield (%)[b]
1	 **3a**	 **4a**	 **5a**	4	81
2	 **3a**	 **4b**	 **5b**	5	84
3	 **3a**	 **4c**	 **5c**	5	78
4	 **3b**	 **4d**	 **5d**	3	83
5	 **3c**	 **4c**	 **5e**	5	78
6	 **3d**	 **4d**	 **5f**	4	85
7	 **3h**	 **4b**	 **5g**	4	85

Table 3 Construction of Arylated/Biarylated/Aryl Alkynylated Pyrido-Fused Tetrahydropyrimidiniums, Diazepaniums, and Diazacaniums **5a–h** and **7a–d** (continued)

Entry	Pyridinium derivative	Boronic acid	Product[a]	Time (min)	Yield (%)[b]
8	 **3e**	 **4c**	 **5h**	4	80
9	 **3a**	 **6a**	 **7a**	6	76
10	 **3a**	 **6b**	 **7b**	5	74
11	 **3c**	 **6a**	 **7c**	6	77
12	 **3c**	 **6b**	 **7d**	6	71

[a] All the reactions were performed at 180 W, using base (1 equiv).
[b] Isolated yield.



Scheme 2 Mechanistic pathway for Suzuki–Miyaura derivatization of pyridinium salts

In conclusion, we have explored the scope of synthesizing arylated, biarylated, and aryl alkynylated pyridine-fused heteroaromatic cations from 2-aminopyridines under microwave irradiation, through the application of Suzuki–Miyaura and Sonogashira cross-coupling reactions. The synthesis of these newly generated cations may lead to the identification of newer heteroaromatics having potential NLO-properties and biological activities. The operational simplicity and general applicability of the methodology, from simpler bicyclic to extended tetracyclic ring systems, make it a useful approach to the synthesis of diversely substituted N-heteroaromatic cations. To the best of our knowledge, this is the first reported synthesis of arylated, biarylated and aryl alkynylated pyridinium compounds with six- to eight-membered diaza-heterocyclic cations as their core moiety.

Melting points were determined with a capillary melting point apparatus and are uncorrected. IR spectra were recorded with a JASCO FTIR (model 410) spectrometer in KBr pellets. MS (ESI; positive mode) was conducted with an LC-ESI-Q-TOF micro Mass spectrometer (Indian Institute of Chemical Biology, Kolkata). The NMR spectra were recorded with a Bruker 300/600 DPX spectrometer operating at 300/600 MHz for ^{1}H and 75/150 MHz for ^{13}C, respectively, with tetramethylsilane (TMS) as an internal standard; the chemical shifts are reported in ppm as δ units. Microwave irradiation was performed with a mono-mode Discover microwave reactor (CEM Corp., Matthews, NC, USA). Pyridine derivatives, basic alumina, dibromoalkanes, *o*-xylene dibromide, boronic acids, aryl acetylenes, and bases were purchased from Aldrich Chemical Ltd (USA). Thin-layer chromatography was performed on pre-coated silica gel 60 F254 aluminum sheets (E. Merck, Germany).

Synthesis of Tetrahydropyrimidinum, Diazepanium, and Diazacanium Templates; General Procedure

The pyridine derivatives **1b–c** (3.3 mmol) and dibromoalkane or benzylic dibromide **2a–e** (6 mmol) were placed in a round-bottomed flask (25 mL) and dissolved in a minimum amount of $CHCl_3$. Basic alumina (0.4 g) was then added to the solution and the organic solvent was then evaporated to dryness under reduced pressure. After fitting the flask with a septum, the mixture was subjected to irradiation in a microwave reactor at 90 °C (180 W) for the appropriate amount of time (reaction monitored by TLC). After completion of the reaction, the reaction mixture was cooled and MeOH was added; the slurry was stirred at r.t. for 10 min, then the mixture was vacuum-filtered through a sintered glass funnel. The filtrate was evaporated to dryness under reduced pressure and the residue was purified by flash chromatography to isolate the product.

To recycle the solid support, the residue obtained after vacuum filtration of the reaction mixture was washed with alkaline water and acetone (2–3 times) and subjected to calcination at 150 °C.

7-Bromo-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrimidin-5-ylium Bromide (3a)

Yield: 87%; brown solid; mp 212–214 °C; R_f 0.36 (EtOAc–MeOH, 30%).

IR (KBr): 1433, 1528, 3502 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.06 (m, 2 H), 3.43 (m, 2 H), 4.23 (m, 2 H), 6.93 (m, 1 H), 7.86 (m, 1 H), 8.27 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 17.5 (CH_2), 38.1 (CH_2), 50.3 (CH_2), 102.9 (C), 116.4 (CH), 139.2 (CH), 143.0 (CH), 150.6 (C).

HRMS (ESI): *m*/*z* [M – Br]$^+$ calcd for $C_8H_{10}N_2Br$: 213.0022; found: 213.0038.

7,9-Dibromo-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrimidin-5-ylium Bromide (3b)

Yield: 82%; white solid; mp 226–228 °C; R_f 0.38 (EtOAc–MeOH, 30%).

IR (KBr): 1451, 1573, 3497 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 2.08 (m, 2 H), 3.48 (m, 2 H), 4.30 (m, 2 H), 8.44 (m, 1 H), 8.56 (m, 1 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 17.3 (CH_2), 39.6 (CH_2), 51.8 (CH_2), 102.5 (C), 109.0 (C), 139.4 (CH), 145.5 (CH), 148.5 (C).

HRMS (ESI): *m*/*z* [M – Br]$^+$ calcd for $C_8H_9N_2Br_2$: 290.9127; found: 290.9108.

8-Bromo-2,3,4,5-tetrahydro-1*H*-pyrido[1,2-*a*][1,3]diazepin-6-ylium Bromide (3c)

Yield: 85%; brown solid; mp 230–232 °C; R_f 0.33 (EtOAc–MeOH, 30%).

IR (KBr): 1392, 1508, 3430 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.78 (m, 2 H), 1.93 (m, 2 H), 4.14 (m, 2 H), 7.00 (m, 1 H), 8.02 (m, 1 H), 8.47 (m, 1 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 28.3 (CH_2), 29.4 (CH_2), 52.3 (CH_2), 60.2 (CH_2), 104.7 (C), 116.6 (CH), 139.7 (CH), 144.6 (CH), 152.8 (C).

HRMS (ESI): *m*/*z* [M – Br]$^+$ calcd for $C_9H_{12}N_2Br$: 227.0178; found: 227.0161.

8,10-Dibromo-2,3,4,5-tetrahydro-1*H*-pyrido[1,2-*a*][1,3]diazepin-6-ylium Bromide (3d)

Yield: 87%; yellow solid; mp 206–208 °C; R_f 0.36 (EtOAc–MeOH, 30%).

IR (KBr): 1360, 1478, 3412 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 1.97 (m, 2 H), 2.09 (m, 2 H), 3.73 (m, 2 H), 4.56 (m, 2 H), 8.52 (m, 1 H), 8.61 (m, 1 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 23.2 (CH_2), 23.7 (CH_2), 44.3 (CH_2), 57.4 (CH_2), 104.5 (C), 111.4 (C), 141.2 (CH), 146.1 (CH), 153.1 (C).

HRMS (ESI): *m*/*z* [M – Br]$^+$ calcd for $C_9H_{11}N_2Br_2$: 304.9283; found: 304.9297.

3-Bromo-5,6,7,8,9,10-hexahydro-10-aza-4a-azoniabenzocyclooctene Bromide (3e)

Yield: 73%; brown solid; mp 188–190 °C; R_f 0.33 (EtOAc–MeOH, 30%).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.44 (m, 2 H), 1.71 (m, 2 H), 1.85 (m, 2 H), 3.55 (m, 2 H), 4.11 (m, 2 H), 7.01 (m, 1 H), 8.01 (m, 1 H), 8.49 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 24.0 (CH_2), 26.2 (CH_2), 31.6 (CH_2), 35.0 (CH_2), 53.0 (CH_2), 104.6 (C), 116.5 (CH), 139.7 (CH), 144.4 (CH), 152.8 (C).

HRMS (ESI): *m*/*z* [M – Br]$^+$ calcd for $C_{10}H_{14}N_2Br$: 241.0335; found: 241.0328.

2-Bromo-6,11-dihydro-5*H*-benzo[*e*]pyrido[1,2-*a*][1,3]diazepin-12-ylium Bromide (3f)

Yield: 89%; white solid; mp 200–202 °C; R_f 0.39 (EtOAc–MeOH, 30%).

IR (KBr): 1363, 1520, 3392 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.86 (m, 2 H), 5.77 (m, 2 H), 6.90 (m, 1 H), 7.46 (m, 4 H), 7.85 (m, 1 H), 8.47 (m, 1 H).

HRMS (ESI): *m*/*z* [M – Br]$^+$ calcd for $C_{13}H_{12}N_2Br$: 275.0178; found: 275.0183.

2,4-Dibromo-6,11-dihydro-5*H*-benzo[*e*]pyrido[1,2-*a*][1,3]diazepin-12-ylium Bromide (3g)

Yield: 78%; white solid; mp 238–240 °C; R_f 0.42 (EtOAc–MeOH, 30%).

IR (KBr): 1377, 1456, 3436 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 4.93 (m, 2 H), 5.52 (m, 2 H), 7.34 (m, 1 H), 7.40 (m, 2 H), 7.48 (m, 1 H), 7.92 (s, 1 H), 8.04 (s, 1 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 48.5 (CH_2), 57.3 (CH_2), 127.5 (2 × CH), 128.0 (CH), 128.6 (CH), 129.8 (C), 129.8 (CH), 134.1 (2 × C), 138.0 (C), 139.4 (CH), 139.4 (C).

HRMS (ESI): *m*/*z* [M – Br]$^+$ calcd for $C_{13}H_{11}N_2Br_2$: 352.9283; found: 352.9289.

1,3-Dibromo-12,13-dihydro-5*H*-13-aza-4a-azoniabenzo[4,5]cyclohepta[1,2-*b*]naphthalene Bromide (3h)
Yield: 73%; yellow solid; mp 186–188 °C; R_f 0.44 (EtOAc–MeOH, 30%).

IR (KBr): 1369, 1493, 3471 cm^{-1}.

^1H NMR (600 MHz, DMSO-d_6): δ = 5.06 (m, 2 H), 5.53 (m, 2 H), 7.54 (m, 2 H), 7.63 (m, 1 H), 7.83 (m, 2 H), 7.92 (m, 2 H), 7.97 (s, 1 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 49.7 (CH_2), 57.0 (CH_2), 125.8 (CH), 126.4 (CH), 126.7 (CH), 126.8 (CH), 127.6 (CH), 127.8 (2 × CH), 132.5 (2 × C), 133.0 (C), 133.4 (2 × C), 136.8 (C), 139.1 (CH), 139.1 (C).

HRMS (ESI): *m*/*z* [M – Br]$^+$ calcd for $C_{17}H_{13}N_2Br_2$: 402.9440; found: 402.9467.

Synthesis of Arylated and Biarylated Pyrido-Fused Tetrahydropyrimidinums, Diazepaniums, and Diazacaniums: General Procedure
Compound **3a** (3 mmol) was taken in a 25 mL round-bottomed flask and anhydrous DMF (5 mL) was added, followed by **4a** (3.3 mmol), [Pd(PPh_3)$_4$] (0.1 mmol), and Na_2CO_3 (3 mmol). The solution was then degassed and back-filled with nitrogen (4–5 times). The flask was fitted with a septum and the mixture was subjected to irradiation in a microwave reactor (CEM, Discover, USA) at 80 °C (180 W) for the appropriate amount of time (reaction monitored by TLC). After completion of the reaction, the reaction mixture was cooled, diluted with MeOH, and vacuum-filtered through a sintered glass funnel. The filtrate was then evaporated to dryness in a rotary evaporator under reduced pressure and the residue was purified by chromatography over neutral alumina, eluting with a mixture of EtOAc–MeOH.

7-(2-Methoxyphenyl)-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrimidin-5-ylium Bromide (5a)
Yield: 81%; brown solid; mp 242–244 °C; R_f 0.14 (MeOH–EtOAc, 30%).

IR (KBr): 1269, 1472, 1533, 3447 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.11 (m, 2 H), 3.17 (s, 3 H), 3.42 (m, 2 H), 4.28 (m, 2 H), 6.99 (m, 2 H), 7.15 (m, 1 H), 7.39 (m, 2 H), 7.94 (m, 1 H), 8.04 (s, 1 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 18.0 (CH_2), 38.0 (CH_2), 50.2 (CH_2), 55.7 (CH_3), 111.9 (CH), 113.8 (CH), 121.0 (CH), 121.9 (C), 123.4 (C), 129.7 (CH), 130.1 (CH), 137.9 (CH), 142.4 (CH), 150.4 (C), 156.3 (C).

HRMS (ESI): *m*/*z* [M – Br]$^+$ calcd for $C_{15}H_{17}N_2O$: 241.1335; found: 241.1354.

7-(4-Methoxyphenyl)-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrimidin-5-ylium Bromide (5b)
Yield: 84%; brown solid; mp 240–242 °C; R_f 0.15 (MeOH–EtOAc, 30%).

^1H NMR (300 MHz, DMSO-d_6): δ = 2.11 (m, 2 H), 3.15 (s, 3 H), 3.44 (m, 2 H), 4.33 (m, 2 H), 7.08 (m, 3 H), 7.59 (m, 2 H), 8.15 (m, 2 H), 8.50 (br s, 1 H).

^{13}C NMR (150 MHz, D_2O): δ = 15.3 (CH_2), 35.5 (CH_2), 48.0 (CH_2), 52.7 (CH_3), 111.8 (2 × CH), 112.3 (CH), 122.0 (C), 124.0 (2 × CH), 124.4 (C), 131.7 (CH), 136.7 (CH), 147.5 (C), 156.3 (C).

HRMS (ESI): *m*/*z* [M – Br]$^+$ calcd for $C_{15}H_{17}N_2O$: 241.1335; found: 241.1342.

7-Naphthalen-2-yl-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrimidin-5-ylium Bromide (5c)
Yield: 78%; brown solid; mp 226–228 °C; R_f 0.12 (MeOH–EtOAc, 30%).

^1H NMR (600 MHz, DMSO-d_6): δ = 2.07 (m, 2 H), 3.48 (m, 2 H), 4.25 (m, 2 H), 7.24 (d, *J* = 9.6 Hz, 1 H), 7.07 (m, 1 H), 7.56 (m, 1 H), 7.73 (m, 1 H), 7.87 (m, 2 H), 7.97 (m, 1 H), 8.05 (m, 1 H), 8.32 (m, 1 H), 8.51 (s, 1 H), 9.69 (br s, 1 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 18.0 (CH_2), 37.9 (CH_2), 50.0 (CH_2), 114.7 (CH), 123.5 (C), 123.8 (CH), 124.6 (CH), 126.6 (CH), 126.9 (CH), 127.7 (CH), 128.1 (CH), 128.9 (CH), 131.6 (C), 132.4 (C), 133.2 (C), 139.4 (CH), 140.8 (CH), 151.6 (C).

HRMS (ESI): *m*/*z* [M – Br]$^+$ calcd for $C_{18}H_{17}N_2$: 261.1386; found: 261.1394.

7,9-Bis(4-chlorophenyl)-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrimidin-5-ylium Bromide (5d)
Yield: 83%; yellowish solid; mp 241–242 °C; R_f 0.13 (MeOH–EtOAc, 30%).

^1H NMR (300 MHz, DMSO-d_6): δ = 2.12 (m, 2 H), 3.46 (m, 2 H), 4.37 (m, 2 H), 7.53 (m, 1 H), 7.57 (m, 3 H), 7.62 (m, 2 H), 7.79 (m, 2 H), 7.98 (s, 1 H), 8.40 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 17.9 (CH_2), 35.8 (CH_2), 57.8 (CH_2), 126.9 (C), 127.7 (2 × CH), 129.1 (2 × CH), 129.2 (2 × CH), 131.3 (2 × CH), 132.6 (C), 132.9 (C), 133.2 (C), 133.9 (C), 136.5 (CH), 138.5 (CH), 150.1 (2 × C).

HRMS (ESI): *m*/*z* [M – Br]$^+$ calcd for $C_{20}H_{17}N_2Cl_2$: 355.0763; found: 355.0757.

8-Naphthalen-2-yl-2,3,4,5-tetrahydro-1*H*-pyrido[1,2-*a*][1,3]diazepin-6-ylium Bromide (5e)
Yield: 78%; brown solid; mp 236–238 °C; R_f 0.16 (MeOH–EtOAc, 30%).

IR (KBr): 1483, 1511, 3429 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.01 (m, 2 H), 2.18 (m, 2 H), 3.63 (m, 2 H), 4.63 (m, 2 H), 7.19 (m, 1 H), 7.58 (m, 2 H), 7.86 (m, 1 H), 7.98 (m, 2 H), 8.07 (m, 1 H), 8.27 (s, 1 H), 8.39 (s, 1 H), 8.62 (s, 1 H), 8.90 (br s, 1 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 24.2 (CH_2), 24.5 (CH_2), 43.0 (CH_2), 56.1 (CH_2), 117.5 (CH), 123.8 (CH), 124.8 (CH), 125.7 (C), 126.7 (CH), 126.9 (CH), 127.7 (CH), 128.1 (CH), 128.9 (CH), 131.3 (C), 132.5 (C), 133.1 (C), 138.9 (CH), 140.1 (CH), 155.5 (C).

HRMS (ESI): *m*/*z* [M – Br]$^+$ calcd for $C_{19}H_{19}N_2$: 275.1543; found: 275.1549.

8,10-Bis(4-chlorophenyl)-2,3,4,5-tetrahydro-1*H*-pyrido[1,2-*a*][1,3]diazepin-6-ylium Bromide (5f)
Yield: 85%; yellowish solid; mp 243–245 °C; R_f 0.15 (MeOH–EtOAc, 30%).

^1H NMR (600 MHz, $CDCl_3$): δ = 1.98 (m, 2 H), 2.14 (m, 2 H), 3.44 (m, 2 H), 4.77 (m, 2 H), 7.35 (m, 5 H), 7.40 (m, 2 H), 7.48 (m, 1 H), 7.76 (m, 1 H), 7.99 (s, 1 H), 9.39 (br s, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 21.8 (CH_2), 22.6 (CH_2), 35.0 (CH_2), 54.8 (CH_2), 128.3 (2 × CH), 129.4 (2 × CH), 129.5 (2 × CH), 129.8 (C), 130.8 (2 × CH), 131.8 (C), 134.0 (C), 135.0 (C), 135.3 (C), 139.2 (CH), 142.1 (CH), 155.6 (2 × C).

HRMS (ESI): *m*/*z* [M – Br]$^+$ calcd for $C_{21}H_{19}N_2Cl_2$: 369.0920; found: 369.0934.

1,3-Bis(4-methoxyphenyl)-12,13-dihydro-5*H*-13-aza-4a-azoniabenzo[4,5]cyclohepta[1,2-*b*]naphthalene Bromide (5g)
Yield: 85%; brown solid; mp 246–248 °C; R_f 0.24 (MeOH–EtOAc, 30%).

^{1}H NMR (600 MHz, DMSO-d_6): δ = 3.79 (s, 3 H), 3.82 (s, 3 H), 5.02 (m, 2 H), 6.05 (m, 2 H), 7.04 (m, 2 H), 7.07 (m, 2 H), 7.39 (m, 2 H), 7.58 (m, 2 H), 7.66 (m, 2 H), 7.74 (s, 1 H), 7.89 (s, 1 H), 7.97 (m, 2 H), 8.20 (s, 1 H), 8.50 (s, 1 H).

HRMS (ESI): *m*/*z* [M – Br]$^+$ calcd for $C_{31}H_{27}N_2O_2$: 459.2067; found: 459.2091.

3-Naphthalen-2-yl-5,6,7,8,9,10-hexahydro-10-aza-4a-azoniabenzocyclooctene Bromide (5h)
Yield: 80%; brown solid; mp 216–218 °C; R_f 0.15 (MeOH–EtOAc, 30%).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.54 (m, 2 H), 1.89 (m, 2 H), 2.16 (m, 2 H), 3.87 (m, 2 H), 4.76 (m, 2 H), 7.17 (m, 1 H), 7.55 (m, 2 H), 7.92 (m, 3 H), 8.06 (m, 1 H), 8.23 (m, 1 H), 8.37 (s, 1 H), 8.44 (s, 1 H), 9.12 (br s, 1 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 19.1 (CH_2), 28.3 (CH_2), 29.7 (CH_2), 42.7 (CH_2), 54.9 (CH_2), 117.6 (CH), 123.8 (CH), 124.7 (CH), 125.1 (C), 125.8 (CH), 126.4 (CH), 126.6 (CH), 127.5 (CH), 128.3 (CH), 131.3 (C), 132.4 (C), 133.1 (C), 138.7 (CH), 139.2 (CH), 154.8 (C).

HRMS (ESI): *m*/*z* [M – Br]$^+$ calcd for $C_{20}H_{21}N_2$: 289.1699; found: 289.1682.

Synthesis of Aryl Alkynylated Pyrido-Fused Tetrahydropyrimidinums and Diazepaniums; General Procedure
Aryl acetylene **6a** or **6b** (3 mmol) was taken in a 25 mL round-bottomed flask and anhydrous DMF (5 mL) was added, followed by CuI (3 mmol) and Na_2CO_3 (3 mmol). The solution was then degassed and back-filled with nitrogen (4–5 times) and stirred at r.t. for 10 min (generation of a yellow color). Pyridinium cation **3a** or **3c** (3 mmol), $Pd(OAc)_2$ (0.1 mmol), and Ph_3P (0.2 mmol) were added to the reaction mixture and the solution was degassed and back-filled with nitrogen (4–5 times). The flask was then fitted with a septum and the mixture was subjected to irradiation in a microwave reactor (CEM, Discover, USA) at 80 °C (180 W) for the appropriate amount of time (reaction monitored by TLC). After completion of the reaction, the reaction mixture was cooled, diluted with MeOH, and vacuum-filtered through a sintered glass funnel. The filtrate was then evaporated to dryness in a rotary evaporator under reduced pressure and the residue was purified by chromatography over neutral alumina, eluting with a mixture of EtOAc–MeOH.

7-Phenylethynyl-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrimidin-5-ylium Bromide (7a)
Yield: 76%; brown oil; R_f 0.15 (MeOH–EtOAc, 30%).

^{1}H NMR (600 MHz, DMSO-d_6): δ = 2.10 (m, 2 H), 3.56 (m, 2 H), 4.26 (m, 2 H), 7.04 (m, 1 H), 7.45 (m, 3 H), 7.53 (m, 2 H), 7.82 (m, 1 H), 8.30 (m, 1 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 17.7 (CH_2), 38.3 (CH_2), 50.5 (CH_2), 83.9 (C), 91.1 (C), 106.4 (C), 115.2 (CH), 121.6 (C), 129.0 (2 × CH), 129.4 (CH), 131.4 (2 × CH), 141.9 (CH), 142.5 (CH), 150.7 (C).

HRMS (ESI): *m*/*z* [M – Br]$^+$ calcd for $C_{16}H_{15}N_2$: 235.1230; found: 235.1219.

7-(4-Fluorophenylethynyl)-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrimidin-5-ylium Bromide (7b)
Yield: 74%; brown oil; R_f 0.16 (MeOH–EtOAc, 30%).

^{1}H NMR (600 MHz, DMSO-d_6): δ = 2.10 (m, 2 H), 3.38 (m, 2 H), 4.27 (m, 2 H), 6.99 (m, 1 H), 7.31 (m, 2 H), 7.60 (m, 2 H), 7.95 (s, 1 H), 8.32 (m, 1 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 17.6 (CH_2), 38.2 (CH_2), 50.4 (CH_2), 83.6 (C), 90.0 (C), 106.3 (C), 115.1 (CH), 116.2 (CH), 116.4 (CH), 118.0 (C), 133.6 (CH), 141.9 (CH), 142.6 (CH), 150.7 (C), 161.5 (C), 162.4 (CH).

HRMS (ESI): *m*/*z* [M – Br]$^+$ calcd for $C_{16}H_{14}FN_2$: 253.1136; found: 253.1157.

8-Phenylethynyl-2,3,4,5-tetrahydro-1*H*-pyrido[1,2-*a*][1,3]diazepin-6-ylium Bromide (7c)
Yield: 77%; brown oil; R_f 0.14 (MeOH–EtOAc, 30%).

^{1}H NMR (600 MHz, DMSO-d_6): δ = 1.85 (m, 2 H), 1.98 (m, 2 H), 3.62 (m, 2 H), 4.00 (m, 2 H), 7.10 (m, 1 H), 7.36 (m, 1 H), 7.45 (m, 3 H), 7.53 (m, 1 H), 7.68 (m, 1 H), 8.32 (m, 1 H), 9.15 (br s, 1 H).

HRMS (ESI): *m*/*z* [M – Br]$^+$ calcd for $C_{17}H_{17}N_2$: 249.1386; found: 249.1397.

8-(4-Fluorophenylethynyl)-2,3,4,5-tetrahydro-1*H*-pyrido[1,2-*a*][1,3]diazepin-6-ylium Bromide (7d)
Yield: 71%; brown oil; R_f 0.15 (MeOH–EtOAc, 30%).

^{1}H NMR (600 MHz, DMSO-d_6): δ = 3.07 (m, 2 H), 3.22 (m, 2 H), 3.43 (m, 2 H), 4.16 (m, 2 H), 7.02 (m, 1 H), 7.29 (m, 1 H), 7.60 (m, 1 H), 7.76 (m, 2 H), 7.88 (m, 1 H), 8.45 (m, 1 H), 8.95 (br s, 1 H).

HRMS (ESI): *m*/*z* [M – Br]$^+$ calcd for $C_{17}H_{16}FN_2$: 267.1292; found: 267.1273.

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