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Synthesis of Phenanthridine Derivatives by Microwave-Mediated Cyclization of *o*-Furyl(allylamino)arenes

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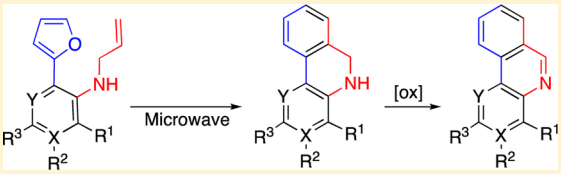
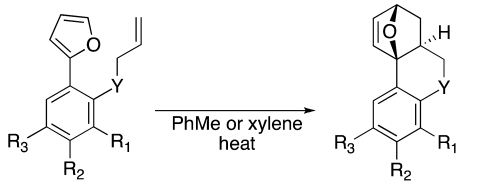
Supporting Information

ABSTRACT: A novel and efficient synthesis of phenanthridines and aza analogues is reported. The key step is a microwave-mediated intramolecular Diels–Alder cyclization of *o*-furyl(allylamino)arenes. In the presence of a catalytic amount of acid, the DA-adduct reacts further to give the dihydrophenanthridines, which easily can be oxidized to fully aromatic compounds by air in the presence of UV light or by DDQ.



The phenanthridine ring system is found in a wide range of bioactive natural products,[1] and synthetic compounds of medicinal interest, some examples are phototherapeutic[2] and platinum complex[3] anticancer compounds, anti-infectives including antituberculosis[4] and antitrypanosomiasis[5] compounds, and PET tracers.[6] We have previously shown that allylamino- or allyloxy-furyl(hetero)arenes can undergo intramolecular Diels–Alder reaction on furans (IMDAF) reactions to give complex fused polycyclic heterocycles (Scheme 1).[7] The

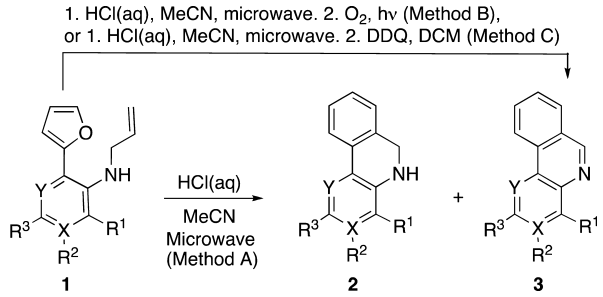
Scheme 1. Diels–Alder Cyclization of *o*-Furyl(allylamino)arenes or -Allyloxyarenes[7]



reactivity of the substrates was highly dependent on the detailed substitution pattern; a substituent *ortho* to the allylic side chain ($R_1 \neq H$, Scheme 1) was shown to have very positive influence on reactivity in the cyclization. Our theoretical studies revealed that the increased reactivity of *ortho*-substituted compounds is mainly due to a steric effect, which destabilizes the minimum conformation of the reactant compared to the active conformations.[7] In order to improve the reaction with respect to less reactive starting materials, we have now turned to microwave chemistry, which to some extent has been applied in IMDAF reactions before.[8] We herein report that not only was the reactivity in the Diels–Alder reaction greatly improved, also it is possible to carry out one-pot syntheses of dihydrophenanthridine and aza analogues, if the reaction is carried out in the presence of acid.

Allylaminofurylarenes or -heteroarenes **1**, previously reported or synthesized by the same protocol as known compounds,[7] were heated under microwave conditions (Scheme 2, Table 1).

Scheme 2. Microwave-Mediated Cyclization of *o*-Furyl(allylamino)arenes 2



An initial screening of solvents showed that degassed MeCN was an excellent reaction medium. Degassing of solvents was found to be of critical importance for high yields to be realized; if the reaction solvent was not degassed, yields were lower due to breakdown of reagents during the heating process. When pure MeCN was employed, the reaction stopped at the Diels–Alder adduct stage, but in the presence of a catalytic amount of aq HCl, the initially formed DA-adduct spontaneously underwent ring opening and subsequent aromatization to afford the dihydrophenanthridines or aza analogues **2**. Some of the dihydro compounds **2** were partly oxidized to the fully aromatic compounds **3** during workup and purification, but the total yields of compounds **2** and **3** were generally high even for substrates **1a**, **1c**, **1d**, **1h**, and **1l**, which did not undergo the IMDAF reaction under conventional heating.[7] Electron-withdrawing substituents, especially R_1 = Cl, seem to stabilize the dihydro(aza)phenanthridines. Only **3a**, **3c**, **3d**, and **3h** were formed in significant amounts by spontaneous oxidation during purification of the dihydro compounds **2**.

We searched for a mild and convenient method for oxidation of the dihydro(aza)phenanthridines **2** to the fully aromatic compounds **3**. First we tried to bubble air thru the reaction

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Table 1. Reaction Times and Yields of Dihydrophenanthridines 2 and Phenanthridines 3

						Method A				Method B		Method C	
entry	X	Y	R^1	R^2	R^3	time (h)	temp (°C)	yield[a] (%) **2**	yield[a] (%) **3**	time (h)	yield[a] (%) **3**	time (h)	yield[a] (%) **3**
1	C	CH	H	H	H	5	170	55, **2a**	14, **3a**	4	63, **3a**	0.5	69, **3a**
2	C	CH	Cl	H	H	1	150	71, **2b**	5, **3b**	3	87, **3b**	0.5	90, **3b**
3	C	CH	H	Cl	H	4	160	63, **2c**	20, **3c**	3	83, **3c**	0.5	67, **3c**
4	C	CH	H	H	Cl	4	160	62, **2d**	29, **3d**	1	91, **3d**	0.5	86, **3d**
5	C	CH	Cl	H	Cl	1	125	95, **2e**		5	86, **3e**	0.25	87, **3e**
6	C	CH	Cl	H	NO_2	1	100	92, **2f**		72	45, **3f**	2	69, **3f**
7	N	CH	Cl		H	1	180	80, **2g**	3, **3g**	6	92, **3g**	4	57, **3g**
8	C	N	H	H	H	5	170	61, **2h**	29, **3h**	3	73, **3h**	0.5	78, **3h**
9	C	N	Cl	H	H	1	150	86, **2i**	9, **3i**	6	75, **3i**	0.5	85, **3i**
10	C	N	H	Cl	H	4	160	80, **2j**		3	81, **3j**	0.5	77, **3j**
11	N	N	Cl		H	6	100	86, **2k**		48	68, **3k**	5	73, **3k**
12	N	N	H		Cl	4	170	88, **2l**		16	61, **3l**	0.5	85, **3l**

[a]Yield of isolated products.

mixture directly after complete microwave cyclization. We soon realized that the reaction was sensitive to light and found that expeditious oxidation could be achieved if the reaction was performed with exposure to UV light (315−400 nm, Method B, Scheme 2, Table 1). Compounds **2** could be converted to the (aza)phenanthridines **3** generally in high yield, although some substrates required prolonged reaction times. Table 2

Table 2. Oxidation of Compound 2i to Compound 3i

	reaction conditions			
entry	atm	light	time (h)	% **3i**[a]
1	air	dark[b]	19	4
2	air	UV light[c]	3.5	100
3	Ar	UV light[c]	3.5	18

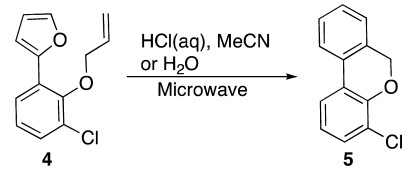
[a]Formation as determined by ^{1}H NMR. [b]Reaction was carried out in a dark box. [c]315−400 nm.

summarizes initial attempts to oxidize compound **2i** and demonstrates the importance of both air and UV light for efficient oxidation (entry 2). Interestingly, oxidation took place, although slower, in the presence of UV light but in the absence of air (entry 3). Photo-induced formation of phenanthridines by cyclization of *N*-(*o*-halobenzyl)arylamines followed by oxidation of the dihydrophenanthridine is reported before, but in these cases it is not absolutely clear whether the final oxidation takes place in the course of the reaction or during workup/purification.[9] However, if the latter is true, the dihydrophenanthridines described in the literature are substantially more prone to oxidation under workup conditions compared to our compounds **2**.

As an alternative to the light-induced air oxidation, we have also shown that all dihydro(aza)phenanthridines **2** can be oxidized to compounds **3** by treatment with DDQ (Method C, Scheme 2, Table 1). The isolated yields were generally high and the reaction times shorter compared to the air oxidation; however, removal of DDQ was problematic in some cases.

During the course of our study, a related microwave-mediated cyclization of *o*-furyl(allyloxy)arenes to afford benzo[*c*]chromenes was published.[10] Here the cyclization took place in water without the addition of any acid to aid in the further transformation of the Diels−Alder adduct intermediate. Our initial screening of solvents for the cyclization of compound **2a** included both water and water−MeCN (1:1), but in both cases no products could be isolated mostly due to insolubility of the starting material in these solvents. However, we tried the microwave-promoted cyclization of the allyloxy derivative **4** (Scheme 3) both in water and in MeCN in the presence of

Scheme 3. Microwave-Mediated Synthesis of the 6*H*-Benzo[*c*]chromene 5



acid, close to the procedure reported for other allyloxy derivatives.[10] In the literature they claim to have run their reactions at rather harsh conditions of 150 °C and 300 W. These conditions were not possible to repeat in our oven, so we set the temperature to 150 °C. The power was ca. 600 W for a few min, while the temperature rose to 150 °C. After reaching the desired temperature, the power was stabile at ca. 15−20 W. When the reaction was carried out in degassed water, there were solubility problems and clumps of dark oily residue on the walls of the reaction flask. All starting material **4** seemed to be consumed, but the product **5** was isolated in only 16%, probable due to extensive decomposition. The compound **4** easily cyclized in MeCN, and the chromene **5** was isolated almost pure in ca. 80% yield after chromatography. An analytical sample (39%) was prepared by recrystallization.

Finally, we explored the posibility of utilizing the microwave-promoted cyclization for the formation of the pyrrolo[3,2,1-*de*]phenanthridine ring skeleton and aza analogues. This tetracyclic ring system is found in several alkaloids including 3,4-dehydroanhydrolycorine (Scheme 4).[11] Compounds **6** were cyclized under microwave conditions in the presence of a catalytic amount of acid. The yield of **7b** was lower than that for **7a**, which is not unexpected. Compound **6b** also reacted with great difficulties to give Diels−Alder adduct under conventional heating without acid.[7]

In conclusion, we have developed an efficient protocol for the microwave-mediated cyclization of *o*-furyl(allylamino)-arenes to dihydrophenanthridines. MeCN was found to be an excellent reaction medium and a catalytic amount of acid was required for further transformations of the Diels−Alder adduct intermediate. The products can readily be oxidized to fully

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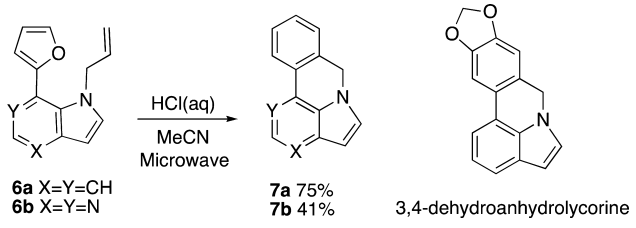
Scheme 4. Microwave-Mediated Synthesis of the Tetracyclic Compounds 7



aromatic compounds by air in the presence of UV light or by DDQ.

EXPERIMENTAL SECTION

General. ^{1}H NMR spectra were recorded at 600, 500, 400, 300, or 200 MHz. The decoupled ^{13}C NMR spectra were recorded at 150, 125, 100, or 75 MHz. All *J* values are reported in hertz. HRMS-EI was performed with a double-focusing magnetic sector instrument and HRMS-ESI with a TOF quadrupole instrument. Microwave experiments were carried out in sealed vessels in a synthesis reactor Monowave 300, Anton Paar GmbH, equipped with a Ruby thermometer and internal IR probe. Flash chromatography was performed on silica gel (Merck no. 09385). The UV lamp was emitting at 315−400 nm with peaks at 352 and 368 nm. HPLC grade MeCN was degassed by freeze−pump−thaw cycling using N_2(l) and flushed with Ar. Physical data for known compounds were in agreement with those reported before.

***N*-Allyl-2,4-dichloro-6-(furan-2-yl)aniline (1e).** $Pd(OAc)_2$ (141 mg, 0.630 mmol), PPh_3 (816 mg, 3.11 mmol), potassium furan-2-yltrifluoroborate (3.30 g, 19.0 mmol), K_2CO_3 (2.50 g, 18.7 mmol), and 2-bromo-4,6-dichloroaniline (3.00 g, 12.5 mmol) in absolute EtOH (200 mL) and water (10 mL) was stirred at reflux under Ar for 3 h. The solvents were removed *in vacuo*, and the product was purified by flash chromatography with EtOAc−DCM−hexane (1:4:45); yield 2,4-dichloro-6-(furan-2-yl)aniline 2.59 g (92%). Mp 66−68 °C, crystalline. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 1.8, 0.8, 1H), 7.36 (d, *J* = 2.4, 1H), 7.22 (d, *J* = 2.4, 1H), 6.63 (dd, *J* = 3.4, 0.8, 1H), 6.53 (dd, *J* = 3.4, 1.8, 1H), 4.65 (s, 2H, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.5, 142.2, 138.6, 128.2, 125.8, 122.3, 120.9, 118.0, 111.7, 108.1; HRMS (EI) calcd for $C_{10}H_7Cl_2NO$ 226.9905, found 226.9903. 2,4-Dichloro-6-(furan-2-yl)aniline (1.04 g, 4.58 mmol), 18-crown-6-ether (1.80 g, 6.82 mmol) and KH (630 mg, ca. 5.50 mmol, ca. 35% in mineral oil) in dry toluene (100 mL) was stirred for 10 min under Ar at rt. Allyl bromide (665 mg, 5.50 mmol) was added, and the mixture was stirred at 35 °C for 2 h. Water (50 mL) was added, the mixture was extracted with DCM (3 × 50 mL), the organic extracts were dried ($MgSO_4$) and evaporated, and the product was isolated by flash chromatography with EtOAc−DCM−hexane (1:4:45); yield 1.03 g (84%), oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 2.4, 1H), 7.49 (d, *J* = 1.9, 1H), 7.28 (d, *J* = 2.4, 1H), 6.86 (d, *J* = 3.3, 1H), 6.51 (dd, *J* = 3.3, 1.8, 1H), 5.97−5.72 (m, 1H), 5.25−5.04 (m, 2H), 4.04 (bs, 1H), 3.51 (dt, *J* = 6.0, 1.5, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 142.3, 141.1, 135.8, 128.3, 127.9, 127.0, 126.7, 125.1, 116.5, 112.0, 109.8, 50.1; MS EI *m*/*z* (rel %) 271/269/267 (6/50/63, M^+), 252/250/248 (14/74/100), 226 (35); HRMS (EI) calcd for $C_{13}H_{11}Cl_2NO$ 267.0218, found 267.0215.

***N*-Allyl-5-chloro-2-(furan-2-yl)pyridin-3-amine (1j).** 2-Bromo-5-chloropyridin-3-amine (2.00 g, 9.71 mmol) was reacted with potassium furan-2-yltrifluoroborate (2.50 g, 14.4 mmol) for 6 h at 80 °C as described in the first step of **1e** synthesis. The product was purified by flash chromatography with EtOAc−DCM−hexane (1:1:8); yield 5-chloro-2-(furan-2-yl)pyridin-3-amine 1.62 g (86%). Mp 107−108 °C, yellow crystalline. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 2.0, 1H), 7.55 (dd, *J* = 1.8, 0.8, 1H), 7.0−6.99 (m, 2H), 6.57 (dd, *J* = 3.5, 1.8, 1H), 4.75 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 142.3, 140.0, 137.8, 132.5, 130.5, 122.9, 112.0, 109.5; HRMS (EI) calcd for $C_9H_7N_2ClO$ 194.0247, found 194.0244. A solution of 5-chloro-2-(furan-2-yl)pyridin-3-amine (1.22 g, 6.26 mmol), 15-crown-5-ether (2.00 g, 12.5 mmol), and NaH (500 mg, ca. 12.5 mmol, ca. 60% in mineral oil) in dry toluene (100 mL) was stirred at 0 °C for 10 min under Ar. Allyl bromide (1.14 g, 9.42 mmol) was added, and the mixture was stirred at rt for 16 h. Water (50 mL) was added. The mixture was extracted with DCM (2 × 50 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was dissolved in dry toluene (100 mL), heated for 16 h at 90 °C under Ar, evaporated onto SiO_2, and purified by flash chromatography with DCM−EtOAc−hexane (1:4:20); yield 578 mg (39%), yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, *J* = 2.0, 1H), 7.53 (dd, *J* = 1.8, 0.8, 1H), 7.00 (dd, *J* = 3.5, 0.8, 1H), 6.91 (d, *J* = 2.0, 1H), 6.56 (dd, *J* = 3.5, 1.8, 1H), 6.09−5.82 (m, 2H), 5.39−5.12 (m, 2H), 3.92−3.60 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 142.0, 141.4, 135.9, 133.8, 132.7, 131.0, 117.8, 116.9, 111.9, 109.4, 45.7; MS EI *m*/*z* (rel %) 236/234 (33/100, M^+), 207 (15), 178 (12); HRMS (EI) calcd for $C_{12}H_{11}N_2ClO$ 234.0560, found 234.0555.

General Procedure for Synthesis of Compounds 2, 5, and 7 (Method A). A stirring solution of compound **1** and aq HCl (0.5 M, 0.2 equiv) in degassed CH_3CN (15 mL) was flushed with Ar for 15 min in a reactor tube and in the microwave oven (reaction time and temperature, see Table 1). The solvent was removed *in vacuo*, and the product purified by flash chromatography.

5,6-Dihydrophenanthridine (2a). The title compound was synthesized from **1a**[7] (200 mg, 1.00 mmol). DCM−EtOAc−hexane (4:6:15) was used for flash chromatography; yield 100 mg (55%) **2a**, mp 118−121 °C (lit.[12] 126−127) and 25 mg (14%) **3a**.[13]

4-Chloro-5,6-dihydrophenanthridine (2b). The title compound was synthesized from **1b**[7] (115 mg, 0.492 mmol). EtOAc−hexane (1:3) was used for flash chromatography; yield 75 mg (71%) (**2b**) and 5 mg (5%) **3b**.[14] Data for **2b**: mp 93−95 °C, crystalline. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 7.8, 1.0, 1H), 7.59 (dd, *J* = 7.8, 1.5, 1H), 7.31 (app td, *J* = 7.8, 1.4, 1H), 7.29−7.20 (m, 1H), 7.18 (dd, *J* = 7.8, 1.5, 1H), 7.13 (d, *J* = 7.5, 1H), 6.74 (app t, *J* = 7.8, 1H), 4.66 (s, 1H), 4.48 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 132.4, 131.5, 128.8, 127.9, 127.8, 126.3, 123.3, 122.8, 122.1, 119.6, 118.8, 46.1; MS EI *m*/*z* (rel %) 217/215 (18/57, M^+), 214 (100), 151 (18); HRMS (EI) calcd for $C_{13}H_{10}ClN$ 215.0502, found 215.0496.

3-Chloro-5,6-dihydrophenanthridine (2c). The title compound was synthesized from **1c**[7] (300 mg, 1.28 mmol). EtOAc−DCM−hexane (1:4:20) followed by (1:4:5) was used for flash chromatography; yield 175 mg (63%) **2c**, mp 121−123 °C (lit.[15] 120−122) and 56 mg (20%) **3c**.[16]

2-Chloro-5,6-dihydrophenanthridine (2d). The title compound was synthesized from **1d**[7] (110 mg, 0.471 mmol). EtOAc−DCM−hexane (1:4:16) was used for flash chromatography; yield 63 mg (62%) **2d**, mp 65−67 °C (lit.[12] 68−69) and 29 mg (29%) **3d**.[9]

2,4-Dichloro-5,6-dihydrophenanthridine (2e). The title compound was synthesized from **1e** (100 mg, 0.373 mmol). EtOAc−DCM−hexane (1:1:18) was used for flash chromatography; yield 89 mg (95%). Mp 66−68 °C, light-yellow crystalline. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 7.7, 1.4, 1H), 7.56 (d, *J* = 2.3, 1H), 7.33 (app td, *J* = 7.7, 1.4, 1H), 7.29 (dd, *J* = 7.4, 1.3, 1H), 7.20 (d, *J* = 2.3, 1H), 7.14 (dd, *J* = 7.7, 7.4, 1H), 4.62 (s, 1H), 4.48 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.6, 132.3, 130.4, 128.4, 128.0, 128.0, 126.3, 124.0, 123.0, 122.9, 122.1, 119.6, 45.9; MS EI *m*/*z* (rel %) 253/251/249 (5/31/54, M^+), 252/250/248 (14/74/100), 213 (9), 177 (19); HRMS (EI) calcd for $C_{13}H_9Cl_2N$ 249.0112, found 249.0107.

4-Chloro-2-nitro-5,6-dihydrophenanthridine (2f). The title compound was synthesized from **1f**[7] (150 mg, 0.538 mmol). EtOAc−DCM−hexane (1:4:16) was used for flash chromatography; yield 129 mg (92%). Mp 159−162 °C, bright-yellow crystalline. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 2.3, 1H), 8.12 (d, *J* = 2.3, 1H), 7.77 (d, *J* = 7.6, 1H), 7.37 (d, *J* = 7.6, 1H), 7.35−7.29 (m, 1H), 7.13 (d, *J* = 7.4 Hz, 1H), 5.27 (bs, 1H), 4.75 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 138.4, 130.3, 129.2, 129.0, 128.5, 126.5, 124.8, 122.9, 120.6, 118.0, 117.9, 45.5; MS EI *m*/*z* (rel %) 262/260 (21/70, M^+), 261/259 (42/100), 213 (56), 178 (23); HRMS (EI) calcd for $C_{13}H_9N_2O_2Cl$ 260.0353, found 260.0343.

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4-Chloro-5,6-dihydrobenzo[*c*][1,7]naphthyridine (2g). The title compound was synthesized from **1g**[7] (102 mg, 0.435 mmol). EtOAc–DCM–hexane (1:3:9) was used for flash chromatography; yield 75 mg (80%) **2g** and 3 mg (3%) **3g**. Data for **2g**: light-yellow waxy material. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, J = 5.0, 1H), 7.70–7.65 (m, 1H), 7.43 (d, J = 5.0, 1H), 7.40–7.31 (m, 2H), 7.17–7.12 (m, 1H), 4.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 137.9, 137.4, 133.0, 129.9, 129.6, 129.2, 128.2, 126.6, 123.5, 116.6, 45.6; MS EI m/z (rel %) 218/216 (21/67, M^+), 217/215 (42/100), 179 (82), 152 (33); HRMS (EI) calcd for $C_{12}H_9N_2Cl$ 216.0454, found 216.0449.

5,6-Dihydrobenzo[*c*][1,5]naphthyridine (2h). The title compound was synthesized from **1h**[7] (175 mg, 0.874 mmol). EtOAc–DCM–hexane (2:3:5) was used for flash chromatography; yield 97 mg (61%) **2h**, mp 95–97 °C (lit.[17] 89–90) and 46 mg (29%) **3h**.[18]

4-Chloro-5,6-dihydrobenzo[*c*][1,5]naphthyridine (2i). The title compound was synthesized from **1i**[7] (205 mg, 0.874 mmol). EtOAc–DCM–hexane (2:3:20) was used for flash chromatography; yield 163 mg (86%) **2i** and 17 mg (9%) **3i**. Data for **2i**: mp 121–122 °C, crystalline. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (dd, J = 7.5, 1.6, 1H), 7.91 (d, J = 5.1, 1H), 7.37 (app td, J = 7.5, 1.5, 1H), 7.33 (app td, J = 7.5, 1.6, 1H), 7.11 (dd, J = 7.5, 1.4, 1H,), 7.07 (d, J = 5.1, 1H), 4.63 (s, 2H), 4.51 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.3, 138.8, 138.2, 132.8, 131.8, 129.6, 128.2, 126.9, 125.9, 124.2, 123.4, 45.4; MS EI m/z (rel %) 218/216 (17/53, M^+), 217/215 (40/100), 179 (15); HRMS (EI) calcd for $C_{12}H_9ClN_2$ 216.0454, found 216.0448.

3-Chloro-5,6-dihydrobenzo[*c*][1,5]naphthyridine (2j). The title compound was synthesized from **1j** (200 mg, 0.852 mmol). EtOAc–DCM–hexane (2:3:10) was used for flash chromatography; yield 148 mg (80%). Mp 139–141 °C, bright-yellow crystalline. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (dd, J = 7.6, 1.4, 1H), 7.95 (d, J = 2.1, 1H), 7.36 (app td, J = 7.6, 1.3, 1H), 7.30 (app td, J = 7.6, 1.4, 1H), 7.12–7.00 (m, 1H), 6.83 (d, J = 2.1, 1H), 4.53 (s, 2H), 3.99 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.8, 138.7, 138.1, 132.6, 131.7, 131.2, 129.3, 128.2, 125.8, 123.7, 120.1, 45.6; MS EI m/z (rel %) 218/216 (16/51, M^+), 217/215 (38/100), 179 (9), 152 (9); HRMS (EI) calcd for $C_{12}H_9N_2Cl$. 216.0454, found 216.0449.

4-Chloro-5,6-dihydropyrimido[5,4-*c*]isoquinoline (2k). The title compound was synthesized from **1k**[7] (105 mg, 0.446 mmol). EtOAc–DCM–hexane (1:1:3) was used for flash chromatography; yield 83 mg (86%). Mp 162–164 °C, yellow crystalline. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.26–8.23 (m, 1H), 7.41 (ddd, J = 7.0, 4.5, 1.8, 2H), 7.13–7.10 (m, 1H), 4.73 (d, J = 1.7, 2H), 4.41 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.5, 146.3, 143.8, 135.5, 133.7, 131.6, 129.7, 128.4, 126.2, 124.9, 45.1; MS EI m/z (rel %) 219/217 (23/68, M^+), 218/216 (45/100), 180 (69); HRMS (EI) calcd for $C_{11}H_8N_3Cl$ 217.0407, found 217.0400.

2-Chloro-5,6-dihydropyrimido[5,4-*c*]isoquinoline (2l). The title compound was synthesized from **1l**[7] (105 mg, 0.446 mmol). EtOAc–DCM–hexane (2:3:5) was used for flash chromatography; yield 85 mg (88%). Mp 210–212 °C, bright-yellow crystalline. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.01–7.95 (m, 2H), 7.45 (app td, J = 7.5, 1.5, 1H), 7.38 (app td, J = 7.5, 1.3, 1H), 7.22 (dd, J = 7.5, 1.3, 1H), 6.54 (s, 1H), 4.55 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 147.1, 147.0, 143.8, 138.8, 134.6, 131.7, 128.8, 127.9, 126.5, 123.4, 43.6; MS EI m/z (rel %) 219/217 (15/52, M^+), 218/216 (37/100), 180 (9); HRMS (EI) calcd for $C_{11}H_8N_3Cl$ 217.0407, found 217.0404.

General Procedure for Synthesis of the (Aza)-phenanthridines 3 (Method B). Compound **1** was cyclized under microwave conditions (see Method A). The mixture was transferred to a quartz tube, and the microwave tube was washed with CH_3CN (15 mL) and subsequently transferred to the quartz tube. Air was bubbled through the mixture while exposed to UV light (315–400 nm) at rt (reaction times, see Table 1). The solvent was removed *in vacuo*, and the product was purified by flash chromatography.

General Procedure for Synthesis of the (Aza)-phenanthridines 3 (Method C). Compound **1** was cyclized under microwave conditions (see Method A), and the mixture was concentrated *in vacuo*. The residue was dissolved in dry DCM (30 mL) and stirred with DDQ (1.2 equiv) at rt (reaction times, see Table 1). The solvent was removed *in vacuo*, and the product purified by flash chromatography.

Phenanthridine (3a). The title compound was synthesized from **1a**[7] (100 mg, 0.502 mmol, Method B) or (105 mg, 0.527 mmol, Method C). EtOAc–DCM–hexane (4:6:15) was used for flash chromatography; yield 56 mg (63%) Method B, 65 mg (69%) Method C. Mp 104–106 °C (lit.[13] 104–105).

4-Chlorophenanthridine (3b). The title compound was synthesized from **1b**[7] (100 mg, 0.428 mmol, Method B) or (80 mg, 0.34 mmol, Method C). EtOAc–DCM–hexane (6:9:35) was used for flash chromatography; yield 80 mg (87%) Method B, 66 mg (90%) Method C. Mp 115–115.5 °C (lit.[14] 98–100).

3-Chlorophenanthridine (3c). The title compound was synthesized from **1c**[7] (100 mg, 0.428 mmol, Method B) or (200 mg, 0.856 mmol, Method C). EtOAc–DCM–hexane (6:9:35) was used for flash chromatography; yield 76 mg (83%) Method B, 123 mg (67%) Method C. Mp 112–113 °C (lit.[16] 107–108).

2-Chlorophenanthridine (3d). The title compound was synthesized from **1d**[7] (100 mg, 0.428 mmol, Method B) or (140 mg, 0.599 mmol, Method C). EtOAc–DCM–hexane (3:3:14) was used for flash chromatography; yield 83 mg (91%) Method B, 110 mg (86%) Method C. Mp 139–140 °C (lit.[9] 154–157).

2,4-Dichlorophenanthridine (3e). The title compound was synthesized from **1e** (100 mg, 0.373 mmol, Method B) or (110 mg, 0.410 mmol, Method C). EtOAc–DCM–hexane (3:3:14) was used for flash chromatography; yield 80 mg (86%) Method B, 88 mg (87%) Method C. Mp 196–197 °C, crystalline. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.21 (s, 1H), 8.31 (d, J = 8.4, 1H), 8.22 (d, J = 2.3, 1H), 7.97 (d, J = 8.0, 1H), 7.80 (dd, J = 8.4, 7.0, 1H), 7.70 (dd, J = 8.0, 7.0, 1H), 7.67 (d, J = 2.3, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.2, 139.2, 135.3, 132.4, 131.7, 131.1, 129.2, 129.0, 128.8, 126.4, 126.2, 122.1, 120.8; MS EI m/z (rel %) 251/249/247 (12/71/100, M^+), 211 (10), 177 (18); HRMS (EI) calcd for $C_{13}H_7Cl_2N$ 246.9956, found 246.9955.

4-Chloro-2-nitrophenanthridine (3f). The title compound was synthesized from **1f**[7] (261 mg, 0.937 mmol, Method B) or (250 mg, 0.897 mmol, Method C). EtOAc–DCM–hexane (1:1:18) followed by (1:2:6) was used for flash chromatography; yield 108 mg (45%) Method B, 160 mg (69%) Method C. Mp 193–194 °C, crystalline. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (s, 1H), 9.42 (d, J = 2.4, 1H), 8.70 (d, J = 8.4, 1H), 8.66 (d, J = 2.4, 1H), 8.24–8.15 (m, 1H), 8.03 (ddd, J = 8.4, 7.1, 1.4, 1H), 7.94–7.85 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 145.4, 144.0, 136.3, 133.0, 132.5, 129.8, 129.7, 126.8, 125.5, 123.1, 122.6, 117.6; MS EI m/z (rel %) 260/258 (31/100, M^+), 212 (26), 200 (26); HRMS (EI) calcd for $C_{13}H_7N_2O_2Cl$: 258.0196, found 258.0190.

4-Chlorobenzo[*c*][1,7]naphthyridine (3g). The title compound was synthesized from **1g**[7] (140 mg, 0.597 mmol, Method B) or (280 mg, 1.19 mmol, Method C). EtOAc–DCM–hexane (2:3:5) was used for flash chromatography; yield 118 mg (92%) Method B, 145 mg (57%) Method C. Mp 191–193 °C, crystalline. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 (s, 1H), 8.56 (d, J = 8.2, 1H), 8.51 (d, J = 5.5, 1H), 8.26 (d, J = 5.6, 1H), 8.13 (dd, J = 7.9, 1.3, 1H), 7.96 (ddd, J = 8.2, 7.1, 1.3, 1H), 7.93–7.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 153.4, 144.2, 136.6, 132.3, 131.6, 130.6, 130.5, 129.3, 127.8, 122.9, 115.6; MS EI m/z (rel %) 216/214 (40/100, M^+), 179 (70), 152 (35); HRMS (EI) calcd for $C_{12}H_7N_2Cl$ 214.0298, found 214.0299.

Benzo[*c*][1,5]naphthyridine (3h). The title compound was synthesized from **1h**[7] (100 mg, 0.499 mmol, Method B) or (105 mg, 0.524 mmol, Method C). EtOAc–DCM–hexane (2:3:5) was used for flash chromatography; yield 66 mg (73%) Method B, 74 mg (78%) Method C. Mp 95–96 °C (lit.[18] 92–93.5).

4-Chlorobenzo[*c*][1,5]naphthyridine (3i). The title compound was synthesized from **1i**[7] (105 mg, 0.447 mmol, Method B or C). EtOAc–DCM–hexane (6:9:35) was used for flash chromatography; yield 72 mg (75%) Method B, 82 mg (85%) Method C. Mp 143–145 °C, crystalline. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.43 (s, 1H), 9.16 (d, J = 8.2, 1H), 8.87 (d, J = 4.9, 1H), 8.12 (d, J = 8.0, 1H), 7.97 (ddd, J = 8.2, 7.1, 1.4, 1H), 7.86 (ddd, J = 8.0, 7.1, 1.3, 1H), 7.78 (d, J = 4.9, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 149.2, 144.1, 142.7, 136.4, 133.5, 132.1, 129.9, 128.7, 128.3, 124.3, 124.0; MS EI m/z (rel

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%) 216/214 (34/100, M^+), 179 (27), 152 (14); HRMS (EI) calcd for $C_{12}H_7ClN_2$ 214.0298, found 214.0293.

3-Chlorobenzo[*c*][1,5]naphthyridine (3j). The title compound was synthesized from **1j** (100 mg, 0.426 mmol, Method B or C). EtOAc–DCM–hexane (6:9:35) was used for flash chromatography; yield 74 mg (81%) Method B, 70 mg (77%) Method C. Mp 141.5–142 °C, crystalline. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.30 (s, 1H), 9.06 (dd, J = 8.3, 1.2, 1H), 8.89 (d, J = 2.4, 1H), 8.39 (d, J = 2.4, 1H), 8.09–8.02 (m, 1H), 7.93 (ddd, J = 8.3, 7.0, 1.2, 1H), 7.81 (ddd, J = 8.1, 7.0, 1.2, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.6, 148.6, 139.5, 135.9, 133.2, 132.0, 131.2, 129.5, 128.3, 128.1, 123.5; MS EI m/z (rel %) 216/214 (34/100, M^+), 179 (16), 152 (11); HRMS (EI) calcd for $C_{12}H_7N_2Cl$ 214.0298, found 214.0300.

4-Chloropyrimido[5,4-*c*]isoquinoline (3k). The title compound was synthesized from **1k**[7] (100 mg, 0.424 mmol, Method B) or (320 mg, 1.36 mmol, Method C). EtOAc–DCM–hexane (1:1:3) was used for flash chromatography; yield 62 mg (68%) Method B, 214 mg (73%) Method C. Mp 186–187 °C, crystalline. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (s, 1H), 9.22 (s, 1H), 9.21–9.15 (m, 1H), 8.26–8.13 (m, 1H), 8.10–7.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 156.1, 154.4, 147.0, 133.7, 132.6, 131.9, 131.8, 130.1, 128.4, 124.4; MS EI m/z (rel %) 217/215 (34/100, M^+), 180 (62), 153 (38); HRMS (EI) calcd for $C_{11}H_6N_3Cl$ 215.0250, found 215.0245.

2-Chloropyrimido[5,4-*c*]isoquinoline (3l). The title compound was synthesized from **1l**[7] (93 mg, 0.39 mmol, Method B) or (100 mg, 0.424 mmol, Method C). EtOAc–DCM–hexane (4:6:15) was used for flash chromatography; yield 51 mg (61%) Method B, 78 mg (85%) Method C. Mp 185–186 °C, crystalline. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.47 (s, 1H), 9.38 (s, 1H), 9.11 (dd, J = 8.1, 1.5, 1H), 8.16 (dd, J = 7.4, 1.8, 1H), 8.04 (ddd, J = 8.1, 7.4, 1.5, 1H), 8.00 (app td, J = 7.4, 1.5, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.6, 158.2, 156.1, 148.3, 135.1, 132.6, 132.3, 131.0, 130.2, 128.4, 124.3; MS EI m/z (rel %) 217/215 (34/100, M^+), 180 (23), 153 (25); HRMS (EI) calcd for $C_{11}H_6N_3Cl$ 215.0250, found 215.0245.

2-(2-(Allyloxy)-3-chlorophenyl)furan (4). (Furan-2-yl)-tributyltin (4.00 g, 11.2 mmol), $(Ph_3P)_2PdCl_2$ (340 mg, 0.484 mmol), and 1-bromo-3-chloro-2-fluorobenzene (2.00 g, 9.66 mmol) in DMF (100 mL) was stirred at 80 °C under Ar for 2 h and evaporated *in vacuo*. The residue was dissolved in satd KF in THF (100 mL), stirred at rt for 16 h, and evaporated *in vacuo*. The product was purified by flash chromatography with DCM–hexane (1:9); yield 2-(3-chloro-2-fluorophenyl)furan 1.73 g (91%), yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.82–7.64 (m, 1H), 7.52 (d, J = 1.8, 1H), 7.35–7.21 (m, 1H), 7.12 (app t, J = 7.9, 1H), 6.97–6.83 (m, 1H), 6.54 (dd, J = 3.5, 1.8, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9 (d, J_{CF} = 252.8), 147.1, 142.4, 128.7, 124.6, 124.3 (d, J_{CF} = 2.9), 121.7 (d, J_{CF} = 17.8), 120.6 (d, J_{CF} = 12.1), 112.1 (d, J_{CF} = 1.7), 111.0 (d, J_{CF} = 12.2); HRMS (EI) calcd for $C_{10}H_6ClFO$ 196.0091, found 196.0087. 2-(3-Chloro-2-fluorophenyl)furan (530 mg, 2.70 mmol), 15-crown-5-ether (2.30 g, 10.5 mmol), prop-2-en-1-ol (626 mg, 10.8 mmol), and NaH (540 mg, ca. 14.65 mmol, ca. 65% in mineral oil) in dry toluene (80 mL) was stirred under Ar at 0 °C for 10 min and at 50 °C for 3 h. Water (100 mL) was added, the mixture was extracted with DCM (3 × 50 mL), the combined organic extracts were dried ($MgSO_4$) and evaporated, and the product was isolated by flash chromatography with DCM–hexane (1:9); yield 620 mg (98%), oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, J = 7.9, 1.6, 1H), 7.49 (d, J = 1.9, 1H), 7.29 (dd, J = 8.0, 1.6, 1H), 7.11 (app t, J = 7.9, 1H), 7.03 (d, J = 3.4, 1H), 6.51 (dd, J = 3.4, 1.8, 1H), 6.13 (ddt, J = 17.0, 10.5, 5.7, 1H), 5.45 (dd, J = 17.0, 1.5, 1H), 5.30 (dd, J = 10.5, 1.4, 1H), 4.47 (d, J = 5.5, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6, 149.4, 142.1, 133.5, 129.12, 129.08, 126.7, 125.2, 125.0, 118.3, 112.2, 110.5, 73.0; MS EI m/z (rel %) 236/234 (16/51, M^+), 195/193 (18/52), 167/165 (33/100); HRMS (EI) calcd for $C_{13}H_{11}ClO_2$ 234.0448, found 234.0451.

4-Chloro-6*H*-benzo[*c*]chromene (5). Alternative 1: The title compound was synthesized from **4** (1.00 g, 4.27 mmol) and 0.5 M HCl (0.5 equiv). The mixture was heated at 170 °C for 2 h. EtOAc–DCM–hexane (1:1:18) was used for flash chromatography; yield 739 mg nearly pure compound. An analytical sample (356 mg, 39%) was prepared by being recrystallized from hot MeOH. Mp 63–64 °C, needles. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.66 (dd, J = 7.7, 1.3, 1H), 7.62 (dd, J = 7.8, 1.6, 1H), 7.38 (d, J = 7.6, 1H), 7.35–7.28 (m, 2H), 7.18–7.13 (m, 1H), 6.98 (app t, J = 7.9, 1H), 5.21 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6, 131.2, 130.0, 129.6, 128.8, 128.4, 124.9, 124.7, 122.7, 122.5, 122.4, 121.8, 69.1; MS EI m/z (rel %) 218/216 (24/75, M^+), 217/215 (42/100), 181 (12), 152 (31); HRMS (EI) calcd for $C_{13}H_9ClO$ 216.0342, found 216.0335. **Alternative 2:** Compound **4** (349 mg, 1.49 mmol) in degassed water (15 mL) was heated in the microwave oven for 5 h at 150 °C. The cooled mixture was extracted with DCM (3 × 50 mL), the combined organic extracts were dried ($MgSO_4$) and evaporated, and the product was purified by flash chromatography with DCM–hexane (1:9); yield 52 mg (16%).

7*H*-Pyrrolo[3,2,1-*de*]phenanthridine (7a). The title compound was synthesized from **6a**[7] (80 mg, 0.36 mmol) and 0.5 M HCl (0.5 equiv). The mixture was heated at 150 °C for 1.5 h. EtOAc–DCM–hexane (1:4:45) was used for flash chromatography; yield 55 mg (75%). Mp 127–129.5 °C, crystalline. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (dd, J = 7.8, 1.3, 1H), 7.55–7.47 (m, 2H), 7.38–7.31 (m, 1H), 7.27 (td, J = 7.5, 1.3, 1H), 7.18 (dd, J = 7.6, 1.3, 1H), 7.15 (d, J = 3.0, 1H), 7.10 (app t, J = 7.6, 1H), 6.55 (d, J = 3.0, 1H), 5.58 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.6, 130.2, 130.2, 128.0, 127.8, 127.3, 126.19, 126.17, 122.9, 120.8, 120.5, 118.5, 113.7, 102.5, 48.0; MS EI m/z (rel %) 205 (56, M^+), 204 (100), 176 (7); HRMS (EI) calcd for $C_{15}H_{11}N$ 205.0891, found 205.0885. No data reported for **7a**[19] before.

7*H*-Benzo[*f*]pyrimido[4,5,6-*hi*]indolizine (7b). The title compound was synthesized from **6b**[7] (300 mg, 1.33 mmol) and 0.5 M HCl (0.5 equiv). The mixture was heated at 150 °C for 3 h. MeOH–DCM (1:19) was used for flash chromatography; yield 113 mg (41%). Mp 164–166 °C, crystalline. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.81 (s, 1H), 8.30 (dd, J = 7.6, 1.6, 1H), 7.95 (d, J = 3.0, 1H), 7.57 (dd, J = 7.6, 1.6, 1H), 7.55–7.49 (m, 1H), 7.46 (d, J = 7.6, 1H), 6.65 (d, J = 3.0, 1H), 5.72 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 151.9, 146.3, 143.3, 134.9, 133.7, 131.5, 128.2, 128.0, 127.9, 123.4, 101.4, 47.1; MS EI m/z (rel %) 207 (69, M^+), 206 (100), 180 (9); HRMS (EI) calcd for $C_{13}H_9N_3$ 207.0796, found 207.0802.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR and ^{13}C NMR spectra of all compounds reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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