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Note

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A One-Pot Direct Iodination of the Fischer–Borsche Ring Using Molecular Iodine and Its Utility in the Synthesis of 6-Oxygenated Carbazole Alkaloids

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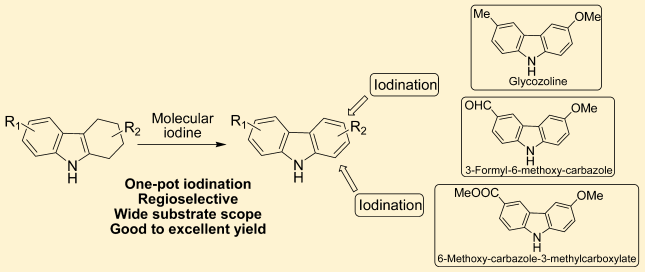
Supporting Information

ABSTRACT: An efficient regioselective iodination of the Fischer–Borsche ring has been achieved using molecular iodine, in a one-pot synthesis. The acid-, metal-, and oxidant-free conditions of the present method are highly convenient and practical. Furthermore, the one-pot direct iodination process is extended to the concise synthesis of glycozoline, 3-formyl-6-methoxy-carbazole, and 6-methoxy-carbazole-3-methylcarboxylate natural alkaloids. This method has been proven to be tolerant to a broad range of functional groups, with good to excellent yields.



Halogenated carbazoles are ubiquitous precursors found in nature and bioactive substances.[1] Significantly, halocarbazoles have been seen to be important in various studies related to material science, such as in the evaluation of photophysical properties of light-emitting carbazoles, in hole-transport materials, conjugated polymers, intense luminescence, organic light-emitting diodes, molecular glasses, and optoelectronics devices.[2]

In general, the introduction of the halo-functionality in the carbazole ring involves two steps: (i) the aromatization of the Fischer–Borsche ring, followed by (ii) the halogenation process (Figure 1). There are several known methods in the literature for the halogenation of carbazoles.[3] However, the bromination and chlorination processes involve the use of potentially hazardous chemicals which are difficult to store and handle. Besides, the combinations of different mineral acids and metal chlorides are decomposed in the halogenation process, producing corrosive side products, creating difficult separation and disposal problems at the end. In this regard, iodination has been found to be the preferable process over bromination and chlorination. Various reports are known in the literature for the iodination of carbazoles, such as IPy_2BF_4/TfOH,[4] KI/KIO_3/AcOH,[5] I_2/$Cu(OAc)_2$/PivOH/MW,[6] CF_3COOAg/ICl/CH_3CN/AcOH,[7] HI/H_2O_2,[8] I_2/$NaIO_4$/H_2SO_4/EtOH, KI/$NaIO_4$/H_2SO_4/EtOH, I_2/$NaIO_4$/AcOH, I_2/NaClO/EtOH, I_2/HgO/EtOH, and NIS/$CHCl_3$.[9] However, these methods require extra oxidants, strong acids, long reaction time,[4,5c] and microwave conditions,[6,8] with several side products that are difficult to separate. They also display poor regioselectivity. The literature survey reveals that the direct iodination of carbazoles is more difficult and most of the methods require the N-protection of carbazoles, followed by iodination.[4,5] Therefore, the development of an oxidant-free protocol for the direct regioselective iodination of tetrahydrocarbazole is highly desirable.

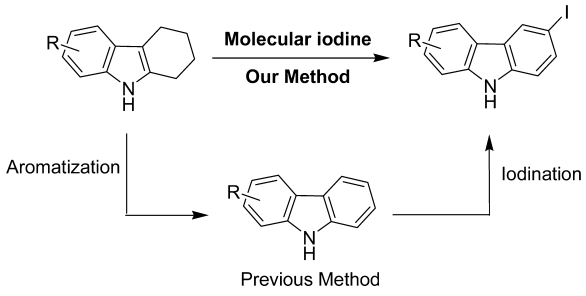


Figure 1. Synthesis of iodocarbazole from tetrahydrocarbazole.

Over the past few decades, molecular iodine has been employed for pharmaceutical and organic syntheses owing to its ready availability as a reagent for organic transformations.[10] In continuation of our previous work devoted toward the development of iodine-mediated transformations,[11] we are interested in developing an efficient protocol for the direct one-pot iodination of tetrahydrocarbazoles using molecular iodine. The present method has been carried out under acid-, metal-, oxidant-free conditions, without the protection of N-carbazole. It is seen to lead to a good regioselectivity. The developed method has been extended to the total synthesis of glycozoline (**7**), 3-formyl-6-methoxy-carbazole (**8**), and 6-methoxy-carbazole-3-methylcarboxylate (**9**).

We commenced our strategy by the condensation of commercially available phenyl hydrazine and cyclohexanone, which were readily converted to the corresponding tetrahydrocarbazole by the Fischer-indolization. We wished to study the

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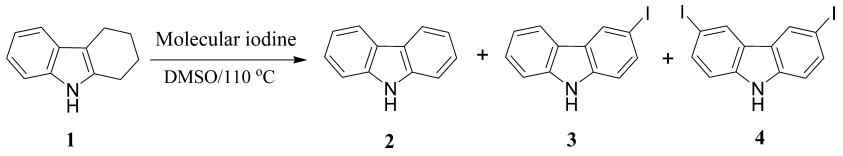
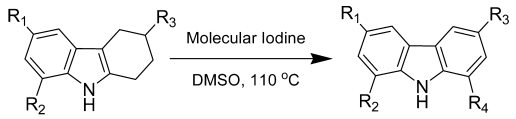
Table 1. Optimization of the Reaction Conditions[a]



entry	iodine (mol %)	temp (°C)	time (h)	yield (%)[b] 2	3	4
a	10	80	24	43[c]	NR[d]	NR
b	25	80	8	95	NR	NR
c	50	80	10	70	30	NR
d	50	110	10	45	50	NR
e	100	110	6	ND[e]	93	NR
f	125	110	10	ND	60	30
g	150	110	8	ND	ND	93[f]

[a]Reaction was carried out with substrate **1a** (1 mmol) and iodine (25 mol %) in DMSO (5 mL) at 110 °C. [b]Isolated yield after column chromatography. [c]Starting substrate was recovered with product. [d]NR indicates no reaction. [e]ND indicates not determined. [f]Product was confirmed by NMR and HRMS.

Scheme 1. Tandem One-Pot Synthesis of Various Iodocarbazoles[a,b]



5a-l 6a-l

Entry	Substrate (5)			Product (6)				Iodine (equiv)	Time (h)	Yield (%)[b]
	R_1	R_2	R_3	R_1	R_2	R_3	R_4			
a	Me	H	H	Me	H	I	H	1	6	95
b	OMe	H	H	OMe	H	I	H	1	6	88
c	Me	Me	H	Me	Me	I	H	1	6	85
d	COOMe	H	H	COOMe	H	I	H	1.5	8	90
e	COOH	H	H	COOH	H	I	H	1.5	8	85
f	CN	H	H	CN	H	I	H	1.5	8	83
g	Cl	H	H	Cl	H	I	H	1.2	6	92
h	Cl	Cl	H	Cl	Cl	I	H	1.2	6	88
i	Cl	H	Me	Cl	I	Me	H	1.5	10	88
j	COOMe	H	Me	COOMe	I	Me	H	2.20	12	87
k	CN	H	Me	CN	I	Me	H	2	11	82
l	COOH	H	Me	COOH	I	Me	H	2.20	12	83

[a]Reaction conditions: Substrate **4** (1 mmol), iodine (100 mol %) in DMSO at 110 °C [b]Isolated yield after column chromatography

efficacy of a one-pot iodination process of tetrahydrocarbazole by molecular iodine. First, when iodine (10−100 mol %) was added to substrate **1**, no remarkable change was observed at room temperature. A catalytic amount of iodine was enough to initiate the reaction at 80 °C (Table 1, entry a). When we increased the amount of iodine (25 mol %), aromatic product (**2**) was isolated in excellent yield (Table 1, entry b). This type of result was found to be in line with our previous report.[12] Further, by increasing the amount of iodine (50 mol %), the mixture of aromatic and monoiodinated products was obtained (Table 1, entry c).

Similarly, when 100 mol % of iodine was employed to substrate **1** at an elevated temperature (110 °C), the monoiodinated

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carbazole was isolated with 93% yield (Table 1, entry e). Additionally, when we investigated with 125 mol % of iodine (Table 1, entry f), the mixture of mono- (60%) and di-iodocarbazole (30%) was isolated. However, the addition of 150 mol % of iodine furnishes di-iodocarbazole as a sole product in 93% yield (Table 1, entry g). Herein, we successfully controlled the formation of aromatic, mono- and di-iodocarbazoles under optimal conditions. From these observations, it is clear that the mol % of iodine and the temperature play important roles in the process of one-pot direct iodination of tetrahydrocarbazole. Compared with other solvents (DCE, CH_3CN, DMF, PhOPh, PhMe, and AcOH), DMSO was found to be a most suitable and effective solvent for the iodination process.

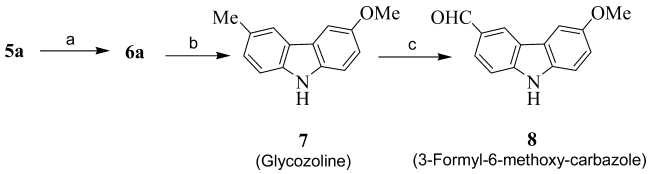
With these optimized conditions, the substrate scope was studied, as shown in Scheme 1. All substrates afforded the corresponding products in good to excellent yield. The iodination process appears to be invariant to the electron-rich and electron-deficient substituents of the tetrahydrocarbazole. We investigated the effect of electron-donating groups at the 3-position of the tetrahydrocarbazole, and the resulting products **6a–c** were isolated in good yield in shorter reaction times (Scheme 1). When electron-withdrawing groups were put at the 3-position of tetrahydrocarbazole, a higher amount of molecular iodine and a longer reaction time were required to complete the iodination process (Scheme 1, entries **6d–h**). This may be due to the characteristic interactive behavior of iodine with the carboxylic group.

However, when we studied the effect of the disubstitution pattern of tetrahydrocarbazole **5** for the iodination process, surprisingly, regioselective iodination was obtained. The careful analysis of products **6i–l** shows that regioselective iodination takes place at the 1-position of tetrahydrocarbazole (Scheme 1). The disappearance of the doublets at 7.26–7.53 ppm and the formation of a characteristic peak at 7.68 ppm in ^{1}H NMR and at 76.1 ppm in ^{13}C NMR analysis support the regioselective iodination at the 1-position of tetrahydrocarbazole.

To exemplify the power of the one-pot iodination process, we carried out a concise synthesis of biologically active 6-oxygenated carbazole alkaloids, such as glycozoline (**7**), 3-formyl-6-methoxy-carbazole (**8**), and 6-methoxy-carbazole-3-methylcarboxylate (**9**). Glycozoline was first isolated from the root bark of *Glycosmis pentaphylla*,[13] and later, it was found in *Murraya koenigii*,[14] *Glycosmis arborea*,[15] *Glycosmis mauritiana*,[16] *Clausena lansium*,[17] and in the roots of the West African tree *Zanthoxylum lemairi*.[18] It exhibits antibiotic and antifungal properties. The 3-formyl-6-methoxy-carbazole (**8**) and 6-methoxy-carbazole-3-methylcarboxylate (**9**) were isolated from the roots of *Clausena lansium*.[19] Later, 3-formyl-6-methoxy-carbazole (**8**) was also isolated from the stem bark of *Micromelum hirsutum* and showed antituberculosis (TB) activity against the H_{37}Rv strain of *Mycobacterium tuberculosis in vitro*.[20] Accordingly, we prepared a synthetic plan to accomplish a series of 6-oxygenated carbazole alkaloids using molecular iodine. A key step of our route is the one-pot synthesis of iodocarbazoles from the tetrahydrocarbazoles using molecular iodine.

Our synthetic strategy for the construction of 6-oxygenated carbazole alkaloids started from the Fischer–Borsche process. The appropriate substrates **5a** and **5c** were prepared by condensation of the commercially available phenyl hydrazine and cyclohexanone under reflux condition. When 3-methyl-tetrahydrocarbazole (**5a**) was subjected to stoichiometric amounts of molecular iodine (one-fold) in DMSO at 110 °C, 3-methyl-6-iodo-carbazole (**6a**) was isolated in excellent yield (95%). In the next step, the iodo group of **6a** was displaced by a methoxy group using NaOMe/CuI[21] in DMF at 120 °C, leading to glycozoline (**7**) in 85% yield. Further, glycozoline (**7**) undergoes the oxidative process when reacted with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[22] in methanol/water medium, leading to the product 3-formyl-6-methoxy-carbazole (**8**) in 90% yield. Thus, 3-formyl-6-methoxy-carbazole (**8**) was obtained in three steps with 73% overall yield (Scheme 2).

Scheme 2. Concise Synthesis of Glycozoline and 3-Formyl-6-methoxy-carbazole[a]

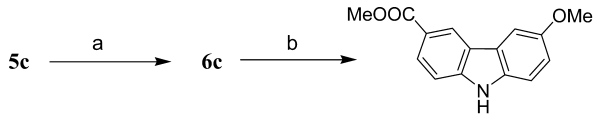


7 (Glycozoline) **8** (3-Formyl-6-methoxy-carbazole)

[a]Reagents and conditions: (a) Iodine (1 equiv), DMSO, 110 °C, 6 h, 95%; (b) NaOMe, CuI, DMF, 120 °C, 12 h, 85%; (c) DDQ, MeOH/H_2O (16:1), rt, 16 h, 90%.

The careful survey of the literature shows that the total synthesis of 6-methoxy-carbazole-3-methylcarboxylate (**9**) was started from the methyl derivative, which subsequently oxidized to the carboxylate group. To the best of our knowledge, there are no reports documented in the literature for the direct use of the carboxylate functionality. In this context, herein, we report the concise synthesis of **9** from the direct use of the ester group as a starting substrate **5c**. In our approach, we started with **5c**, which, upon one-pot iodination by molecular iodine, gave 6-iodo-carbazole-3-methylcarboxylate (**6c**) at 90% yield. This product was treated with NaOMe/CuI[21] in DMF at 120 °C and gave 6-methoxy-carbazole-3-methylcarboxylate (**9**) in two steps with 72% overall yield (Scheme 3).

Scheme 3. Concise Synthesis of 6-Methoxy-carbazole-3-methylcarboxylate[a]



9
6-methoxy-carbazole-3-methylcarboxylate

[a]Reagents and conditions: (a) Iodine (1 equiv), DMSO, 110 °C, 6 h, 90%; (b) NaOMe, CuI, DMF, 120 °C, 12 h, 80%.

In conclusion, we have developed a simple, efficient, and direct process of iodination of tetrahydrocarbazoles using molecular iodine in one-pot. This protocol is equally compatible with electron-deficient and electron-rich groups and affords the desired iodocarbazole in acceptable to excellent yield with good regioselectivity. The application of this method has been successfully extended to the total synthesis of natural products to provide glycozoline (overall yield 61% in two steps), 3-formyl-6-methoxy-carbazole (overall yield 55% in three steps), and 6-methoxy-carbazole-3-methylcarboxylate (overall yield 63% in two steps).

EXPERIMENTAL SECTION

Representative Procedure for the Synthesis of Iodocarbazoles by Molecular Iodine (5a–l). A mixture of iodine (742 mg, 2.92

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mmol) and substituted tetrahydrocarbazole **5a–l** (500 mg, 2.92 mmol) in DMSO (5 mL) was stirred at 110 °C for 8 h. The progress of the reaction was monitored by thin-layer chromatography (PMA was used to strain). The reaction mixture was poured in an ice cold saturated solution of sodium thiosulfate and kept at 0 °C overnight. The solid product was separated out. The crude product was purified by column chromatography using *n*-hexane/ethyl acetate (100:1) as eluent to afford iodocarbazoles **6a–l**.

*3-Iodo-9H-carbazole (**3**).*[23] 811 mg (95%) as a white solid, mp 188–192 °C (lit.[23] mp 191 °C); IR (ν cm^{-1}): 3398, 3040, 1598, 1498, 1440; ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.21 (s, D_2O exchange, 1H), 8.31(s, 1H), 7.96 (d, J = 9.0 Hz, 1H), 7.47 (dd, J_1 = 3.0 Hz, J_2 =3.0 Hz, 1H), 7.33 (d, J = 6.0 Hz, 1H), 7.26 (d, J = 6.0 Hz, 1H), 7.21 (t, J_1 = 3.0 Hz, J_2 = 6.0 Hz, 1H), 7.00 (t, J_1 = 6.0 Hz, J_2 = 6.0 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 139.6, 138.6, 133.2, 128.5, 126.1, 125.0, 121.0, 120.5, 118.8, 113.3, 110.9, 81.2; MS (70 ev) m/z: 292 (M^+), HRMS (ESI-qTOF) Calcd for $C_{12}H_8IN$ $[M + H]^+$, 293.9774: found 293.9770.

*3,6-Diiodo-9H-carbazole (**4**).*[24] 1.139 g (93%) as a white solid, mp 200–202 °C; IR (ν cm^{-1}): 3400, 3040, 1600, 1498, 1445; ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.54 (s, D_2O exchange, 1H), 8.57 (s, 2H), 7.65 (d, J = 9.0 Hz, 2H), 7.35 (d, J = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 138.7, 133.9, 129.1, 123.7, 113.4, 81.8; MS (70 ev) m/z: 418 (M^+), HRMS (ESI-qTOF) Calcd for $C_{12}H_7I_2N$ $[M + H]^+$, 419.8740: found 419.8742.

*3-Iodo-6-methyl-9H-carbazole (**6a**).*[12] 788 mg (95%) as a brown solid, mp 188–190 °C (lit.[12] mp 189 °C); IR (ν cm^{-1}): 3400, 3030, 1595, 1492, 1430; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.34 (s, D_2O exchange, 1H), 8.04 (d, J = 6.0 Hz, 1H), 7.87 (s, 1H), 7.62 (d, J = 9.0 Hz, 1H), 7.40 (s, 1H), 7.30 (t, J_1 = 3.0 Hz, J_2 = 12.0 Hz, 1H), 7.19 (t, J_1 = 3.0 Hz, J_2 = 6.0 Hz, 1H), 2.51 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.0, 142.9, 138.1, 133.5, 133.2, 132.4, 130.2, 126.6, 124.8, 117.6, 115.4, 85.6, 26.1; MS (70 ev) m/z: 306 (M^+), HRMS (ESI-qTOF) Calcd for $C_{13}H_{10}IN$ $[M + H]^+$, 307.9930: found 307.9933.

*3-Iodo-6-methoxy-9H-carbazole (**6b**).* 707 mg (88%) as a white solid, mp 152–158 °C; IR (ν cm^{-1}): 3382, 3060, 1613, 1485, 1454; ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.0 (s, D_2O exchange, 1H), 8.09 (s, 1H), 7.97 (s, 1H), 7.65 (d, J = 9.0 Hz, 1H), 7.60 (d, J = 9.0 Hz, 1H), 7.52 (d, J = 9.0 Hz, 1H), 7.42 (d, J = 6.0 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.6, 139.8, 134.0, 125.8, 123.8, 122.6, 119.9, 118.8, 114.8, 111.7, 103.0, 82.3, 54.4; MS (70 ev) m/z: 322 (M^+), HRMS (ESI-qTOF) Calcd for $C_{13}H_{10}INO$ $[M + H]^+$, 323.9879: found 323.9882.

*3-Iodo-6,8-dimethyl-9H-carbazole (**6c**).* 685 mg (85%) as a yellow solid, mp 137–140 °C; IR (ν cm^{-1}): 3390, 3026, 1598, 1485, 1415; ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.07 (s, D_2O exchange, 1H), 7.47 (s, 1H), 7.31 (s, 1H), 7.28 (s, 1H), 7.17 (d, J = 6.0 Hz, 1H), 6.72 (d, J = 6.0 Hz, 1H), 2.55 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.9, 142.5, 141.3, 138.9, 136.8, 133.2, 129.9, 128.6, 126.2, 123.6, 122.2, 82.0, 20.6, 15.0; MS (70 ev) m/z: 321 (M^+), HRMS (ESI-qTOF) Calcd for $C_{14}H_{12}IN$ $[M + H]^+$, 322.0087: found 322.0090.

*6-Iodo-9H-carbazole-3-methylcarboxylate (**6d**).* 689 mg (90%) as a white solid, mp 220–224 °C; IR (ν cm^{-1}): 3386, 1717, 1600, 1450, 1258; ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.80 (s, D_2O exchange, 1H), 8.80 (s, 1H), 8.63 (s, 1H), 7.98 (dd, J_1 = 3.0 Hz, J_2 = 3.0 Hz, 1H), 7.66 (dd, J_1 = 3.0 Hz, J_2 = 3.0 Hz, 1H), 7.52 (d, J = 6.0 Hz, 1H), 7.35 (d, J = 6.0 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.3, 143.0, 139.9, 134.8, 129.8, 127.8, 125.6, 123.5, 121.5, 120.8, 114.3, 111.5, 83.2, 52.3; MS (70 ev) m/z: 350 (M^+), HRMS (ESI-qTOF) Calcd for $C_{14}H_{10}INO_2$ $[M + H]^+$, 351.9834: found 351.9842.

*6-Iodo-9H-carbazole-3-carboxylic Acid (**6e**).* 666 mg (85%) as a brown solid, mp 254–260 °C; IR (ν cm^{-1}): 3400, 3043, 1603, 1490, 1450, 1260; ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.52 (s, D_2O exchange, 1H), 11.68 (s, D_2O exchange, 1H), 8.72 (s, 1H), 8.54 (s, 1H), 7.93 (d, J = 9.0 Hz, 1H), 7.59 (d, J = 6.0 Hz, 1H), 7.45 (d, J = 9.0 Hz, 1H), 7.29 (d, J = 9.0 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.8, 142.3, 139.4, 134.1, 129.1, 127.5, 125.1, 123.0, 121.4, 120.9, 113.7, 110.7, 82.4; MS (70 ev) m/z: 336 (M^+), HRMS (ESI-qTOF) Calcd for $C_{13}H_8INO_2$ $[M + H]^+$, 337.9672: found 337.9668.

*6-Iodo-9H-carbazole-3-carbonitrile (**6f**).* 673 mg (83%) as a brown solid, mp 186–190 °C; IR (ν cm^{-1}): 3400, 3045, 2225, 1600, 1485, 1450; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.87 (s, D_2O exchange, 1H), 8.37 (s, 1H), 8.09 (s, 1H), 7.75 (d, J = 9.0 Hz, 1H), 7.66 (d, J = 6.0 Hz, 1H), 7.49 (d, J = 9.0 Hz, 1H), 7.30 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.2, 138.9, 135.5, 129.5, 128.9, 127.2, 125.3, 120.7, 113.1, 111.5, 111.1, 102.5, 83.2; MS (70 ev) m/z: 317 (M^+), HRMS (ESI-qTOF) Calcd for $C_{13}H_7IN_2$ $[M + H]^+$, 318.9726: found 318.9722.

*3-Chloro-6-iodo-9H-carbazole (**6g**).*[25] 733 mg (92%) as a white solid, mp 184–186 °C (lit.[25] mp 181–182 °C); IR (ν cm^{-1}): 3395, 3032, 1600, 1496, 1427; ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.56 (s, D_2O exchange, 1H), 8.57 (s, 1H), 8.27 (s, 1H), 7.66 (d, J = 9.0 Hz, 1H), 7.50 (d, J = 9.0 Hz, 1H), 7.41 (t, J_1 = 3.0 Hz, J_2 = 9.0 Hz, 1H), 7.37 (t, J_1 = 3.0 Hz, J_2 = 9.0 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 139.2, 138.0, 134.0, 129.1, 125.9, 124.2, 123.2, 122.3, 120.1, 113.5, 112.4, 81.6; MS (70 ev) m/z: 326 (M^+), HRMS (ESI-qTOF) Calcd for $C_{12}H_7ClIN$ $[M + H]^+$, 327.9384: found 327.9390.

*1, 3-Dichloro-6-iodo-9H-carbazole (**6h**).* 640 mg (88%) as a white solid, mp 164–168 °C; IR (ν cm^{-1}): 3400, 3033, 1590, 1495, 1429; ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.30 (s, D_2O exchange, 1H), 8.60 (s, 1H), 8.23 (s, 1H), 8.05 (s, 1H), 7.65 (d, J = 9.0 Hz, 1H), 7.48 (d, J = 9.0 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 140.3, 138.2, 135.8, 129.9, 125.7, 123.8, 123.2, 122.1, 120.4, 120.0, 113.0, 81.0; MS (70 ev) m/z: 360 (M^+), HRMS (ESI-qTOF) Calcd for $C_{12}H_6Cl_2IN$ $[M + H]^+$, 361.8994: found 361.8996.

*3-Chloro-1-iodo-6-methyl-9H-carbazole (**6i**).* 685 mg (88%) as a white solid, mp 92–96 °C; IR (ν cm^{-1}): 3398, 3032, 1600, 1498, 1429; ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.27 (s, D_2O exchange, 1H), 8.24 (s, 1H), 8.05 (s, 1H), 7.74 (s, 1H), 7.65 (d, J = 9.0 Hz, 1H), 7.48 (dd, J = 9.0 Hz, 1H), 2.50 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 140.3, 138.1, 135.7, 129.8, 125.7, 123.8, 123.2, 122.0, 120.3, 120.0, 113.0, 76.0, 20.3; MS (70 ev) m/z: 340 (M^+), HRMS (ESI-qTOF) Calcd for $C_{13}H_9ClIN$ $[M + H]^+$, 341.9540: found 341.9536.

*1-Iodo-6-methyl-9H-carbazole-3-methylcarboxylate (**6j**).* 653 mg (87%) as a white solid, mp 185–190 °C; IR (ν cm^{-1}): 3386, 3034, 1720, 1600, 1450, 1260; ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.45 (s, D_2O exchange, 1H), 8.72 (s, 1H), 8.07 (s, 1H), 8.00 (d, J = 9.0 Hz, 1H), 7.68 (s, 1H), 7.61 (d, J = 9.0 Hz, 1H), 3.88 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 166.6, 142.5, 140.4, 135.7, 130.6, 126.8, 122.9, 122.7, 122.4, 120.4, 120.3, 111.4, 76.1, 51.6, 20.3; MS (70 ev) m/z: 364 (M^+), HRMS (ESI-qTOF) Calcd for $C_{15}H_{12}INO_2$ $[M + H]^+$, 365.9991: found 365.9993.

*1-Iodo-6-methyl-9H-carbazole-3-carbonitrile (**6k**).* 648 mg (82%) as a brown solid, mp 218–224 °C; IR (ν cm^{-1}): 3400, 3040, 2222, 1600, 1482, 1454; ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.58 (s, D_2O exchange, 1H), 8.59 (s, 1H), 8.00 (s, 1H), 7.72 (dd, J_1 = 3.0 Hz, J_2 = 3.0 Hz, 1H), 7.68 (s, 1H), 7.62 (d, J = 6.0 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 142.3, 141.0, 137.0, 131.4, 129.4, 126.6, 123.3, 122.7, 121.2, 120.9, 113.2, 101.2, 76.9, 21.0; MS (70 ev) m/z: 331 (M^+), HRMS (ESI-qTOF) Calcd for $C_{14}H_9IN_2$ $[M + H]^+$, 332.9883: found 332.9887.

*1-Iodo-6-methyl-9H-carbazole-3-carboxylic Acid (**6l**).* 634 mg (83%) as a brown solid, mp 240–244 °C; IR (ν cm^{-1}): 3400, 3045, 1600, 1495, 1450, 1265; ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.20 (s, D_2O exchange, 1H), 11.41 (s, D_2O exchange, 1H), 8.66 (s, 1H), 8.01 (s, 1H), 7.97 (dd, J = 6.0 Hz, 1H), 7.63 (s, 1H), 7.55 (d, J = 6.0 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.4, 143.0, 141.0, 136.3, 131.0, 127.8, 123.6, 123.4, 122.9, 122.0, 121.0, 111.8, 76.7, 20.9; MS (70 ev) m/z: 350 (M^+), HRMS (ESI-qTOF) Calcd for $C_{14}H_{10}INO_2$ $[M + H]^+$, 351.9828: found 351.9832.

Synthesis of Glycozoline (7) and 6-Methoxy-carbazole-3-methylcarboxylate (9).[21] In a 100 mL round-bottom flask, substrate **6a** (0.100 g, 0.325 mmol), CuI (0.123 g, 0.651 mmol), and DMF (10 mL) were added to a solution of NaOMe, prepared from metallic sodium (0.149 g, 6.5 mmol) and absolute MeOH (1.5 mL). The reaction mixture was refluxed (maintain the temperature of oil bath at 120 °C) for 12 h under an argon atmosphere. After the completion of reaction, EtOAc (30 mL) was added to the reaction mixture and the insoluble materials were filtered through Celite and washed with EtOAc. The filtrate was washed with brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed on a column of silica gel using *n*-hexane/EtOAc (100:2) to give **7** (0.058 g, 85%) as a brown powder.

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*Glycozoline or 3-Methoxy-6-methyl-carbazole (**7**).*[12] 58 mg (85%) as a brown solid, mp 182−184 °C (lit.[12] mp 181−183 °C); IR (ν cm^{-1}): 3400, 3035, 1580, 1485, 1454; ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.8 (s, D_2O exchange, 1H), 7.71 (s, 1H), 7.52 (s, 1H), 6.77−7.23 (m, 3H), 6.58 (d, J = 9.0 Hz, 1H), 3.73 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.9, 138.4, 134.7, 130.8, 126.4, 119.3, 114.1, 110.7, 110.2, 109.3, 102.2, 99.3, 55.3, 22.5; MS (70 ev) m/z: 211 (M^+), HRMS (ESI-qTOF) Calcd for $C_{14}H_{13}NO$ $[M + H]^+$, 212.1069: found 212.1065.

*6-Methoxy-carbazole-3-methylcarboxylate (**9**).*[26] 116 mg (80%) as a white solid, mp 150−152 °C (lit.[26b] mp 147−149 °C); IR (ν cm^{-1}): 3395, 1780, 1670, 1550, 1430, 1258; ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.80 (s, D_2O exchange, 1H), 8.80 (s, 1H), 8.64 (s, 1H), 7.99 (dd, J = 6.0 Hz, 1H), 7.66 (dd, J = 6.0 Hz, 1H), 7.52 (d, J = 6.0 Hz, 1H), 7.35 (d, J = 6.0 Hz, 1H), 3.84 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.0, 142.8, 139.4, 134.6, 129.8, 127.8, 125.3, 123.5, 121.5, 121.0, 115.8, 113.7, 111.3, 55.3, 52.3; MS (70 ev) m/z: 255 (M^+), HRMS (ESI-qTOF) Calcd for $C_{15}H_{13}NO_3$ $[M + H]^+$, 256.0968: found 256.0972.

Synthesis of 3-Formyl-6-methoxy-carbazole (8).[22] In a 100 mL round-bottom flask, substrate **7** (100 mg, 0.473 mmol) was treated with DDQ (537 mg, 2.36 mmol) in MeOH/H_2O (16:2) at room temperature for 4 h, and the progress of the reaction was monitored by thin-layer chromatography. The solvent was evaporated in vacuum. The crude product was purified through column chromatography using *n*-hexane/ethyl acetate to give **8** with 90% yield.

*3-Formyl-6-methoxy-carbazole (**8**).*[22] 95 mg (90%) as a white solid, mp 134−138 °C (lit.[26b] mp 135−136 °C); IR (ν cm^{-1}): 3210, 3040, 1680, 1600, 1530, 1482, 1454; ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.08 (s, D_2O exchange, 1H), 10.11 (s, 1H), 8.08 (s, 1H), 7.85 (s, 1H), 7.30 (d, J = 9.0 Hz, 1 H), 7.24 (d, J = 6.0 Hz, 1H), 6.97 (d, J = 6.0 Hz, 1H), 6.92 (d, J = 9.0 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.8, 138.7, 137.5, 133.8, 129.0, 128.0, 127.0, 125.6, 123.8, 120.2, 119.1, 112.5, 110.5, 52.3; MS (70 ev) m/z: 225 (M^+), HRMS (ESI-qTOF) Calcd for $C_{14}H_{11}NO_2$ $[M + H]^+$, 226.0862: found 226.0865.

■ ASSOCIATED CONTENT

Supporting Information

Characterization data including ^{1}H and ^{13}C NMR spectra. 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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