An Efficient and General Synthesis of Indolo[2,3-*a*]carbazoles Using the Fischer Indole Synthesis

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Abstract: Synthetically important indolo[2,3-*a*]carbazoles were obtained in a one-pot reaction via Fischer indole synthesis starting from 2-amino-cyclohexanone hydrochloride and substituted arylhydrazines hydrochloride in the presence of acidic media.

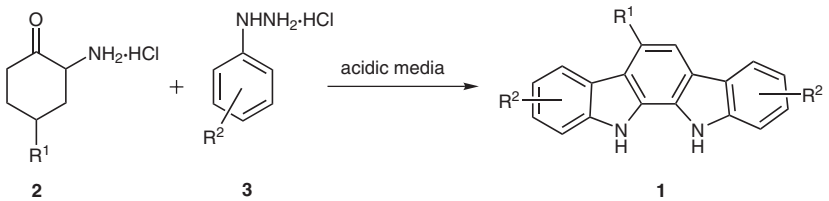
Key words: Fischer indole synthesis, indolo[2,3-*a*]carbazole alkaloids, 2-amino-cyclohexanone, arylhydrazine, heterocycle

Indolo[2,3-*a*]carbazole is the heterocyclic core of several important natural products including the Tjipanazoles (*T. tjipanasensis*),[1] Rebeccamycin (*S. aerocolonigenes*),[2] Staurosporine (*S. staurosporeus*)[3] and their derivatives. The indolo[2,3-*a*]carbazole alkaloids are extremely interesting owing to the wide range of biological activities that they possess, including antifungal,[1,4] hypotensive,[5] and antimicrobial[6] activities, as well as inhibition of protein kinase C (PKC)[3a,7] and platelet aggregation.[3c] The great interest in these compounds, however, has been due to their potent antitumor[4,8] activity. Presently, several indolo[2,3-*a*]carbazole alkaloids are in clinical trials for potential use in cancer therapy.[9] Many synthetic strategies toward the synthesis of indolo[2,3-*a*]carbazole backbone have already been developed. These include, for example, condensation of 8-amino-1,2,3,4-tetrahydro-9-methyl-9*H*-carbazole with 2-hydroxycyclohexanone,[10] cyclization of either 1,2,3,4-tetrahydro-9*H*-carbazol-1-one or the monophenylhydrazone of cyclohexane-1,2-dione with phenylhydrazine via Fischer indole synthesis,[11] cycloaddition of 1,1′-dimethyl-2,2′-bisindolyl with racemic α-chloro-α-phenylacetyl chloride,[12] electrocyclization of 3-substituted indol-2(3*H*)-one or 1-phenylsulfonyl-3-tributylstannylindole,[13] palladium-catalyzed cross-coupling reactions of indole,[14] and [4+2]-cycloaddition of 2,2′-bisindolyl with dimethyl acetylenedicarboxylate or *N*-phenylmaleimide.[15] Despite the number and diversity of these methods, several research strategies have shown modest yields, harsh reaction conditions and/or tedious work up procedures. For this reason, the development of a new and general method for the synthesis of indolo[2,3-*a*]carbazoles is of scientific interest.

We now report a novel tandem Fischer indole synthesis that assembles indolo[2,3-*a*]carbazoles **1** in one step from 2-amino-cyclohexanone hydrochloride **2** and substituted arylhydrazines hydrochloride **3** (Scheme 1). This methodology provides for the rapid construction of a variety of highly substituted indolo[2,3-*a*]carbazoles.

At the first attempt, an equimolar mixture of 2-aminocyclohexanone hydrochloride **2a** and 4-chlorophenylhydrazine hydrochloride **3e** in glacial HOAc was refluxed for 3 h. This yielded a mixture of two products, which were separated and assigned on the basis of its IR spectra, ^{1}H NMR, MS data and microanalyses.[16] One product was 1-oxo-6-chloro-1,2,3,4-tetrahydrocarbazole (**4e**) and the other product was 3,8-dichloroindolo[2,3-*a*]carbazole (**1e**). To realize our objective of one-pot synthesis of indolo[2,3-*a*]carbazoles, we examined the reaction of **2a** with 4 equivalents of **3e** in glacial HOAc to give a single product **1e**. Herein, the plausible mechanism of cyclization of **2** with **3** is considered to be Fischer indole synthesis, plus hydrolysis to 1-oxo-1,2,3,4-tetrahydrocarbazoles **4**, then through the bis-Fischer indole reaction to give 5,6,11,12-tetrahydroindolocarbazoles **5**, which dehydrogenate to obtain target compounds **1** (Scheme 2).

As discussed above on mechanism, the acid strength of the solution in many cases determines the yields in Fischer indole reactions.[17] According to this, we investigated the reaction of **2a** with **3e** by choosing nine different



Scheme 1

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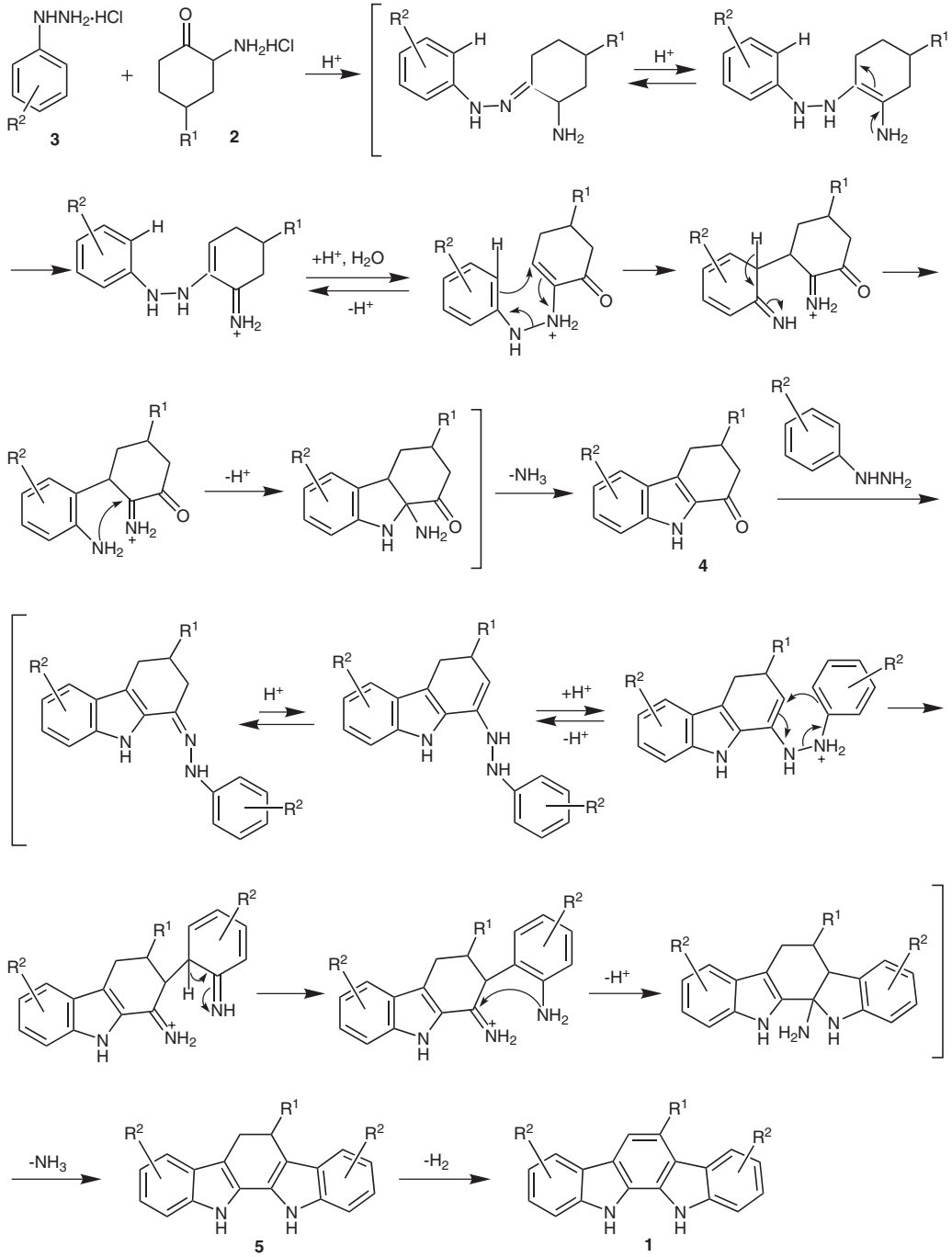


Scheme 2 A plausible reaction mechanism for the synthesis of indolo[2,3-*a*]carbazoles

acidic medium. The results (Table 1) demonstrated that 95% HOAc–TFA or $ZnCl_2$–HOAc were more suitable conditions for the mentioned reaction and the yield of the product **1e** could be improved up to 87% and 86%, respectively. In the presence of 95% HOAc–TFA, the reaction of **2** with a series of substituted arylhydrazine hydrochlorides **3** proceeded in good yields (Table 2).[18,19] However, cyclization of 3-chlorophenylhydrazine hydrochloride (**3g**) with **2a** led to a 2.6:1:1 mixture of 4,7-dichloroindolo[2,3-*a*]carbazole (**1g**), 2,7-dichloroindolo[2,3-*a*]carbazole, 2,9-dichloroindolo[2,3-*a*]carbazole (Scheme 3). In addition, cyclization of the *ortho*-halophenylhydrazines hydrochloride with **2a** under Fischer indole conditions could occur either to the *o*-unsubstituted side of *o*-halophenylhydrazine to give the 'normal' product, 1,10-dihaloindolo[2,3-*a*]carbazole, or to the *o*-substituted side of *o*-halophenylhydrazine to give the 'abnormal' products, 1-haloindolo[2,3-*a*]carbazole and unsubstituted indolo[2,3-*a*]carbazole (Scheme 4). To optimize the regioselectivity of the reaction of **2a** with *o*-halophenylhydrazines hydrochloride **3j–l**, we investigated the reaction by choosing several different conditions,[20] such as *p*-toluenesulfonic acid (TsOH) in ethanol, hydrogen chloride in ethanol, zinc chloride in acetic acid or poly-

phosphoric acid (PPA), which gave unsatisfactory results. At last, the Fischer indolization of **2a** with *o*-bromophenylhydrazine hydrochloride **3l** was successfully carried out with PrOH and glacial HOAc to give only the normal 1,10-dibromoindolo[2,3-*a*]carbazole (**1l**, Table 2, entry 12),[21] but unfortunately under the same condition, the reaction of **2a** with *o*-chlorophenylhydrazine hydrochloride **3k** gave a 6:1:1 mixture of the normal 1,10-dichloroindolo[2,3-*a*]carbazole (**1k**), the abnormal 1-chloroindolo[2,3-*a*]carbazole and indolo[2,3-*a*]carbazole (**1a**) in 80% overall yield (Table 2, entry 11), and the reaction of **2a** with *o*-fluorophenylhydrazine hydrochloride (**3j**) obtained the mixture of 1,10-difluoroindolo[2,3-*a*]carbazole **(1j)**, 1-fluoroindolo[2,3-*a*]carbazole and indolo[2,3-*a*]carbazole (**1a**) in 71% overall yield and ca. 3:3:1 ratio (Table 2, entry 10). It was apparent from the results with *o*-bromo, *o*-chloro and *o*-fluoro groups that the less electron-attractive halo group resulted in a higher ratio of normal products to abnormal products.

Table 1 Results of the Fischer Indolization of 2-Aminocyclohexanone Hydrochloride (**2a**) with *p*-Chlorophenylhydrazine Hydrochloride (**3e**) in Various Acid Catalysts

Entry	Acid catalyst	Reaction temp (°C)	Reaction time (h)	Yield (%)[a]
1	95% HOAc–TFA	100	12	87
2	Glacial HOAc	Reflux	14	83
3	HCOOH (97%)	Reflux	13	72
4	$ZnCl_2$–HOAc	Reflux	21	86
5	$BF_3{\cdot}OEt_2$–HOAc	Reflux	5	46
6	*p*-TsOH–EtOH	Reflux	20	69
7	[BMIM][Al_2Cl_7][b]	180	0.5	30
8	PCl_3–CH_2Cl_2	Reflux	10	0[c]
9	HCl–EtOH	Reflux	12	12

[a] Isolated yield.
[b] A chloroaluminate ionic liquid, [*N*-butyl-*N*-methylimidazolium][Al_2Cl_7].
[c] No reaction had occurred.

Table 2 Reaction of 2-Aminocyclohexanone Hydrochlorides **2** with Arylhydrazine Hydrochlorides **3**[a]

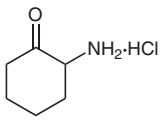
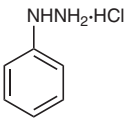
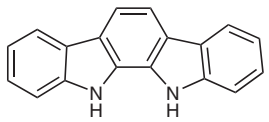
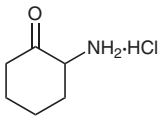
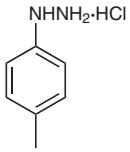
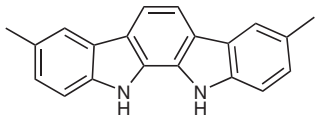
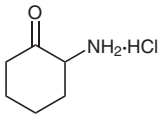
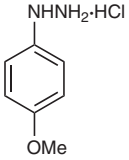
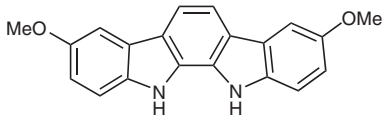
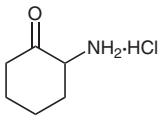
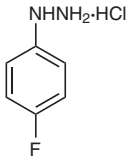
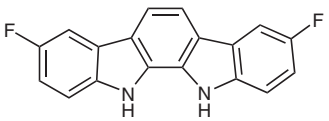
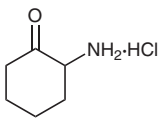
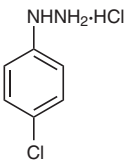
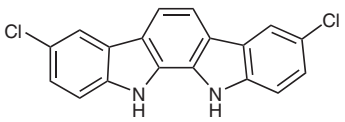
Entry	**2**	**3**	Product **1**	Yield[b] (%)
1	 **2a**	 **3a**	 **1a**	94
2	 **2a**	 **3b**	 **1b**	86
3	 **2a**	 **3c**	 **1c**	52
4	 **2a**	 **3d**	 **1d**	65
5	 **2a**	 **3e**	 **1e**	87

Table 2 Reaction of 2-Aminocyclohexanone Hydrochlorides **2** with Arylhydrazine Hydrochlorides **3**[a] (continued)

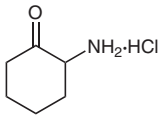
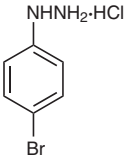
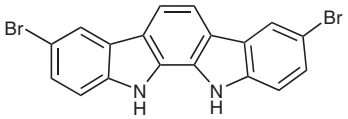
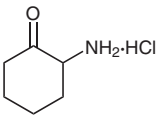
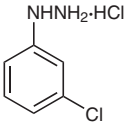
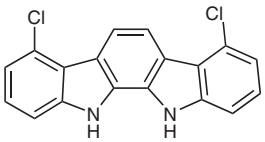
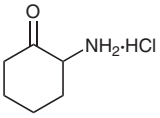
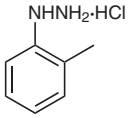
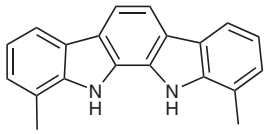
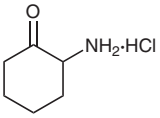
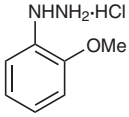
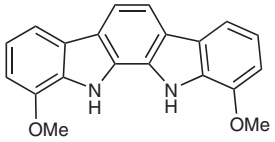
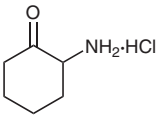
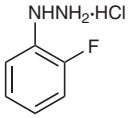
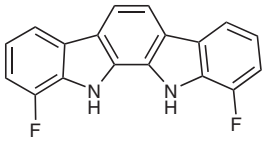
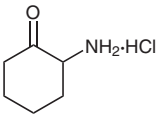
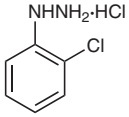
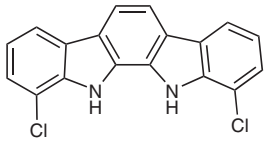
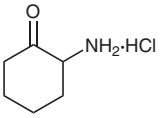
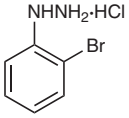
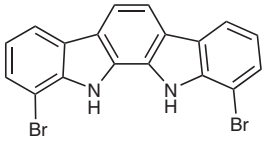
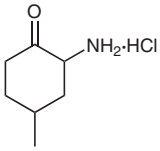
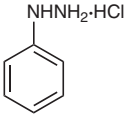
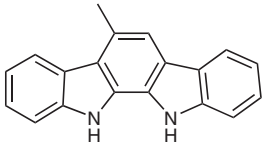
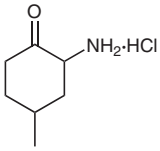
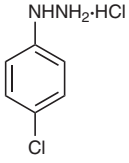
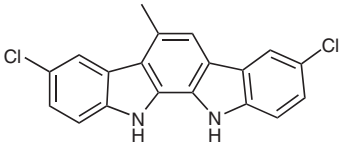
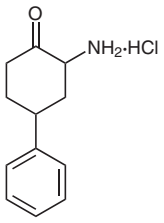
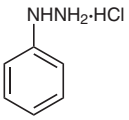
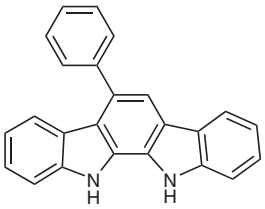
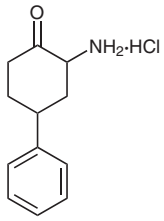
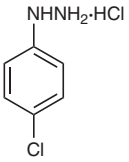
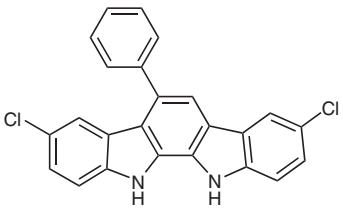
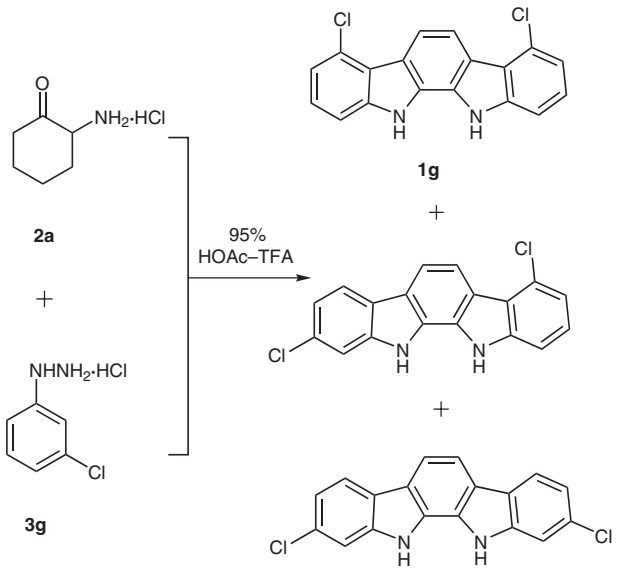
Entry	**2**	**3**	Product **1**	Yield[b] (%)
6	 **2a**	 **3f**	 **1f**	65
7	 **2a**	 **3g**	 **1g**	82[c]
8	 **2a**	 **3h**	 **1h**	48
9	 **2a**	 **3i**	 **1i**	48
10	 **2a**	 **3j**	 **1j**	71[d]
11	 **2a**	 **3k**	 **1k**	80[e]
12	 **2a**	 **3l**	 **1l**	51
13	 **2b**	 **3a**	 **1m**	92
14	 **2b**	 **3e**	 **1n**	86

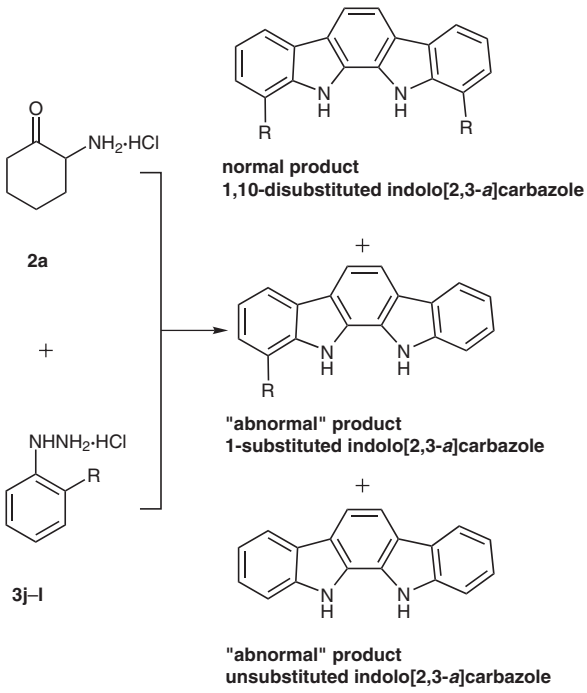
Table 2 Reaction of 2-Aminocyclohexanone Hydrochlorides **2** with Arylhydrazine Hydrochlorides **3**[a] (continued)

Entry	2	3	Product **1**	Yield[b] (%)
15	 **2c**	 **3a**	 **1o**	88
16	 **2c**	 **3e**	 **1p**	71

[a] All reactions took place in 95% HOAc–TFA (see ref.[18]), except for entries 10–12, which performed in the presence of PrOH and glacial HOAc (see ref.[21]).
[b] Isolated yield.
[c] A 2.6:1:1 mixture of 4,7-dichloroindolo[2,3-*a*]carbazole (**1g**), 2,7-dichloroindolo[2,3-*a*]carbazole and 2,9-dichloroindolo[2,3-*a*]carbazole.
[d] A 3:3:1 mixture of 1,10-difluoroindolo[2,3-*a*]carbazole (**1j**), 1-fluoroindolo[2,3-*a*]carbazole and indolo[2,3-*a*]carbazole (**1a**).
[e] A 6:1:1 mixture of 1,10-dichloroindolo[2,3-*a*]carbazole (**1k**), 1-chloroindolo[2,3-*a*]carbazole and indolo[2,3-*a*]carbazole (**1a**).



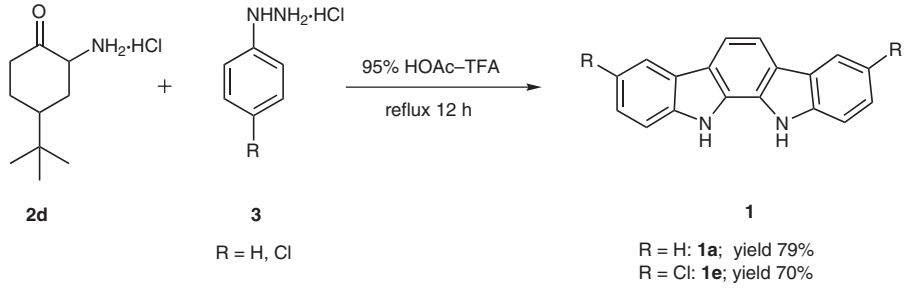
Scheme 3



Scheme 4

To our surprise, the reaction of 2-amino-4-*tert*-butylcyclohexanone hydrochloride (**2d**) with substituted phenylhydrazines hydrochloride in the presence of 95% HOAc–TFA did not give the desired product, 5-*tert*-butylindolo[2,3-*a*]carbazoles, but afforded indolo[2,3-*a*]carbazoles which lost *tert*-butyl group (Scheme 5).

In summary, we have established a novel and one-pot route to synthesize several indolo[2,3-*a*]carbazole derivatives from easily available 2-amino-cyclohexanone hydrochloride and substituted arylhydrazines hydrochloride using Fischer indole synthesis, which proceeds smoothly under mild conditions. Apart from experimental simplicity, the advantage of this methodology is the insensitivity of the reaction mixture towards air and moisture. Synthetic study aimed at broadening the scope of this potentially useful reaction is in progress.



Scheme 5

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(16) (a) **Spectral Data for 1-Oxo-6-chloro-1,2,3,4-tetrahydrocarbazole (4e)**: mp 218 °C (lit.[22] mp 220 °C). IR (KBr): 3269.91, 3065.63, 2944.19, 2867.84, 1652.68, 1539.99, 1481.58, 810.98, 734.34 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.27–2.32 (m, 2 H, CH_2), 2.67 (t, *J* = 6.0 Hz, 2 H, CH_2), 2.98 (t, *J* = 5.6 Hz, 2 H, CH_2), 7.32–7.38 (m, 2 H, ArH), 7.65 (s, 1 H, ArH), 8.97 (s, 1 H, NH). MS (EI): *m/z* = 221 [M + 2], 219 [M^+]. Anal. Calcd for $C_{12}H_{10}ClNO$: C, 65.61; H, 4.59; N, 6.38. Found: C, 65.49; H, 4.51; N, 6.25. (b) **Spectral Data for 3,8-Dichloroindolo[2,3-*a*]carbazole (1e):** mp >300 °C (lit.[1] mp >300 °C). IR (KBr): 3404.88, 3078.94, 1570.63, 1492.32, 875.91, 811.22 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 11.25 (s, 2 H, NH), 8.24 (d, *J* = 1.6 Hz, 2 H, H-4, H-7), 7.95 (s, 2 H, H-5, H-6), 7.70 (d, *J* = 8.4 Hz, 2 H, H-1, H-10), 7.37 (dd, *J* = 8.4, 2.0 Hz, 2 H, H-2, H-9). MS (EI): *m/z* = 327 [M + 2], 325 [M^+]. Anal. Calcd for $C_{18}H_{10}Cl_2N_2$: C, 66.48; H, 3.10; N, 8.61. Found: C, 66.35; H, 3.07; N, 8.42.

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(18) **General Procedure for Indolo[2,3-*a*]carbazoles (1a–i, 1m–p):**
The 2-amino-cyclohexanone hydrochloride **2** (0.334 mmol) and substituted arylhydrazine hydrochloride **3** (4 equiv) were dissolved in 1.5 mL 95% HOAc and 0.5 mL TFA. The mixture was heated to 100 °C until TLC analysis showed complete consumption of the intermediate 1-oxo-1,2,3,4-tetrahydrocarbazoles **4**. The mixture was cooled to r.t., H_2O was added and the solid was collected by filtration. The crude products were purified by chromatography on silica gel using petroleum ether–EtOAc (5:1) as eluant. The yields in Table 2 represent the average of two or more runs.

(19) All new compounds gave satisfactory analytical and spectral data. Data for selected compounds are as follows:
Compound **1o** (Table 2, entry 15): mp >300 °C. IR (KBr): 3357.15, 3300.33, 3054.31, 1695.67, 1599.14, 1488.63, 740.66 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 11.24 (s, 1 H, NH), 11.04 (s, 1 H, NH), 8.14 (d, *J* = 7.6 Hz, 1 H, Ar-H), 7.73 (s, 1 H, Ar-H), 7.66 (t, *J* = 7.6 Hz, 2 H, Ar-H), 7.62 (d, *J* = 7.6 Hz, 2 H, Ar-H), 7.54 (t, *J* = 7.6 Hz, 2 H, Ar-H), 7.47 (t, *J* = 7.2 Hz, 1 H, Ar-H), 7.37 (t, *J* = 7.6 Hz, 1 H, Ar-H), 7.28–7.32 (m, 2 H, Ar-H), 7.16 (t, *J* = 7.6 Hz, 1 H, Ar-H), 6.90 (t, *J* = 7.6 Hz, 1 H, Ar-H). MS (EI): *m/z* = 332 [M^+]. Anal. Calcd for $C_{24}H_{16}N_2$: C, 86.72; H, 4.85; N, 8.43. Found: C, 86.61; H, 4.78; N, 8.35.
Compound **1p** (Table 2, entry 16): mp >300 °C. IR (KBr): 3419.72, 3355.40, 1703.65, 1567.85, 1455.51, 806.60, 704.63 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 11.53 (s, 1 H, NH), 11.32 (s, 1 H, NH), 8.31 (s, 1 H, Ar-H), 7.85 (s, 1 H, Ar-H), 7.74–7.78 (m, 2 H, Ar-H), 7.60–7.66 (m, 4 H, Ar-H), 7.54 (t, *J* = 6.4 Hz, 7.2 Hz, 1 H, Ar-H), 7.42 (d, *J* = 8.4 Hz, 1 H, Ar-H), 7.35 (d, *J* = 8.4 Hz, 1 H, Ar-H), 7.23 (s, 1 H, Ar-H). MS (EI): *m/z* = 403 [M + 2], 401 [M^+]. Anal. Calcd for $C_{24}H_{14}Cl_2N_2$: C, 71.83; H, 3.52; N, 6.98. Found: C, 71.69; H, 3.45; N, 6.83.

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(21) **General Procedure for the Synthesis of Compounds (1j–l):**
The 2-amino-cyclohexanone hydrochloride **2a** (50 mg, 0.334 mmol) was added to a solution of *ortho*-halophenyl-hydrazines hydrochloride **3j–l** (4 equiv) in *n*-propyl alcohol (2 mL) at r.t., then the reaction mixture was refluxed for 3 h. The solvent was removed in vacuo, glacial HOAc (3 mL) was added to the residue, and the mixture was refluxed for 12 h. The mixture was cooled to r.t., H_2O was added and the solid was collected by filtration. The crude products were purified by chromatography on silica gel using petroleum ether–EtOAc (15:1) as eluant. The results are depicted in Table 2 (entries 10–12).

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