Furan Ring Opening – Indole Ring Closure: Synthesis of Furo[2',3':3,4]-cyclohepta[1,2-*b*]indolium Chlorides

Alexander V. Butin*, Sergey K. Smirnov and Tatyana A. Stroganova

Kuban State University of Technology, Moskovskaya st. 2, Krasnodar, 350072, Russia.
E-mail: alexander_butin@mail.ru

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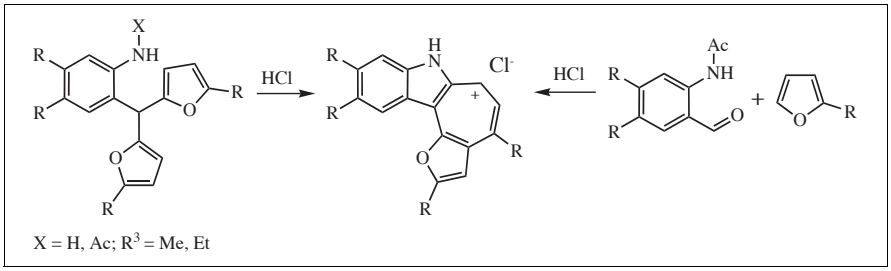

A new synthetic approach to furo[2',3':3,4]cyclohepta[1,2-*b*]indolium chlorides is elaborated starting from 2-acetylaminoaryldifurylmethanes or 2-aminoaryldifurylmethanes under treatment with methanolic HCl solution. The reaction proceeds in three steps: recyclization, intramolecular cyclization, and disproportionation. In this case the furan ring takes part in building up both pyrrole and seven-membered rings. The same salts can be obtained directly from 2-acetylaminobenzaldehydes and 2-methylfuran under similar conditions without isolation of corresponding 2-acetylaminoaryldifurylmethanes.

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Introduction.

A great number of indole derivatives possessing diverse biological and pharmaceutical activities are annulated with five-, six, and seven-membered carbocycles. Among the 2,3-condensed derivatives a remarkable amount of attention is devoted to azaazulenes (cyclohepta[*b*]indoles) which are constituents of some alkaloids [1] and pigments [2]. These compounds show a wide range of biological activity including anti-inflammatory [3], anticancer [4], antitumor [5] and are affecting central nervous system [6].

The biological activity of cyclohepta[*b*]indoles contributed to the development of plenty of synthetic approaches to their synthesis. There are two main approaches among them: 1) formation of pyrrole part of indole; 2) formation of carbocyclic fragment. For a long time one of the most popular approaches to the pyrrole ring construction of indoles has been provided by the Fischer synthesis based on transformation of corresponding phenylhydrazones [7]. Another one applied to the synthesis of fused indole derivatives is the Bischler method [8].

The indoles condensed with seven-membered cycle are usually obtained by reaction of *o*-iodoanilines with cycloheptanone in the presence of palladium acetate [9] or by palladium-mediated cross-coupling of 2-functionalized nitroarenes with α-halo-enones followed by the reductive N-heteroannelation [10]. An interesting example of the pyrrole ring formation is the synthesis of indole tricyclic derivative under the modified Bartoli reaction conditions: the interaction of nitroarenes with an excess of the corresponding Grignard reagent [11].

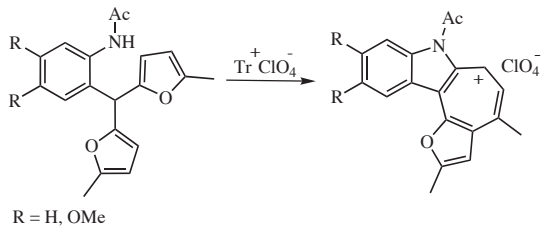
In recent years the second approach to the fused indoloazulenes has been rapidly developing. It involves the annelation of carbocyclic fragment to the preformed indole moiety [12].

Thus inter- and intramolecular cyclizations catalyzed by transition metals (palladium, in particular) are used widely [13,2b]. Among examples of the intramolecular cyclization leading to the formation of carbocyclic fragment of azaazulenes the following should be mentioned: the carbenoid insertion [14], the cascade addition-cyclization reaction of indolyl radicals generated from phenyl selenoesters [15] and intramolecular cyclization of indolylborates [16]. A convenient approach to the carbocycle construction is provided by the intramolecular condensation of corresponding indole derivatives in the PPA medium or under the treatment with $(CF_3CO)_2O$ in the presence of BF_3 [17].

However, the synthetic routes to condensed cyclohepta-[*b*]indoles with the transformations of furan ring are scarce.

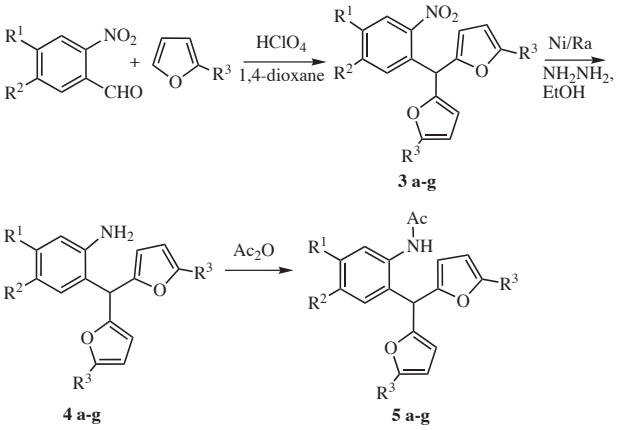
We have developed an efficient approach to the synthesis of condensed heterocyclic systems such as benzofurans, indoles, isochromenones and isoquino-

Scheme 1



linones based on recyclization of furan ring in substituted benzylfurans [18]. Earlier we reported on the synthesis of planar tetracyclic tropylium salts (Scheme 1) [19]. The obtained salts incorporate cyclohepta[*b*]indole fragment and are potential biologically active compounds. However, the presence of perchlorate-anion makes them unsuitable for biological activity investigations. Keeping this in mind, we planned to substitute the perchlorate-anion in tetracyclic indole salts by another pharmaceutically acceptable counter-ion such as chloride-ion [4a] and to synthesize new salts of this type.

Scheme 2



3, 4, 5	R^1	R^2	R^3
a	H	H	Me
b	OMe	OMe	Me
c	OMe	OMe	Et
d	O H_2O		Me
e	O H_2O		Et
f	O H_2 H_2O		Me
g	Br	H	Me

Table 1

Physical Data of Compounds **5**

Comp.	mp	Yield	Mol. Formula	Calcd. (Found) %		
				C	H	N
5a	136-137	60	$C_{19}H_{19}NO_3$ (309.37)	73.77 (73.94)	6.19 (6.04)	4.53 (4.79)
5b	143-144	66	$C_{21}H_{23}NO_5$ (369.42)	68.28 (68.40)	6.28 (6.43)	3.79 (3.96)
5c	93-94	56	$C_{23}H_{27}NO_5$ (397.48)	69.50 (69.68)	6.85 (6.98)	3.52 (3.73)
5d	165-166	69	$C_{20}H_{19}NO_5$ (353.38)	67.98 (68.16)	5.42 (5.64)	3.96 (3.79)
5e	134-135	57	$C_{22}H_{23}NO_5$ (381,43)	69.28 (69.41)	6.08 (6.32)	3.67 (3.85)
5f	156-157	69	$C_{21}H_{21}NO_5$ (367.41)	68.65 (68.49)	5.76 (5.93)	3.81 (3.99)
5g	158	62	$C_{19}H_{18}BrNO_3$ (388.26)	58.78 (58.54)	4.67 (4.88)	3.61 (3.50)

Results and Discussion.

For this purpose we have obtained *o*-aminoaryldifurylmethanes **4** by condensation of the *o*-nitrobenzaldehydes **1** with 2-alkylfurans **2** and subsequent reduction of formed *o*-nitrobenzylfurans **3** (Scheme 2). The interaction of the compounds **4** with acetic anhydride resulted in *o*-acetylaminobenzylfurans **5** (Table 1, 3).

The passing of the gaseous hydrogen chloride through methanolic solutions of the compounds **5** resulted in their recyclization leading to tetracyclic indole salts **6** (method A, Table 2, 3). It has been found that under conditions employed the recyclization proceeds with the loss of the acetyl group (Scheme 3). It is of interest that salts **6** can be obtained directly from the amines **3**, omitting the acetylation step.

From our point of view the mechanism of the formation of tetracyclic structure includes intermediate formation of

Table 2

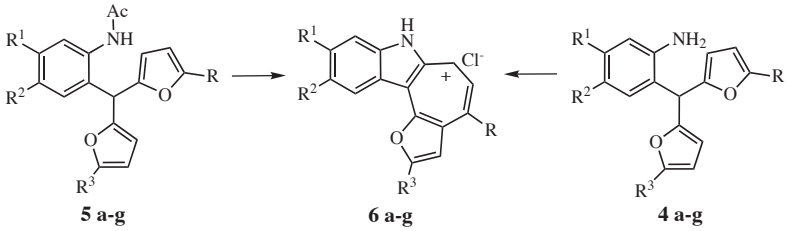
Physical Data of Compounds **6**

Comp.	mp (°C) (with decomp.)	Yield (%) Method A	Yield (%) Method B	Mol. Formula (Mol. Wt)	Calcd. (Found) % C	H	N
6a	200-202	40		$C_{17}H_{14}ClNO$ (283.76)	71.96 (72.09)	4.97 (4.79)	4.94 (4.85)
6b	203-205	58	39	$C_{19}H_{18}ClNO_3$ (343.81)	66.38 (66.52)	5.28 (5.15)	4.07 (4.00)
6c	198-199	47		$C_{21}H_{22}ClNO_3$ (371.87)	67.83 (67.72)	5.96 (6.09)	3.77 (3.83)
6d	243-245	63	25	$C_{18}H_{14}ClNO_3$ (327.77)	65.96 (65.99)	4.31 (4.27)	4.27 (4.30)
6e	177-179	54		$C_{20}H_{18}ClNO_3$ (355.82)	67.51 (67.54)	5.10 (5.12)	3.94 (3.96)
6f	205-206	54	19	$C_{19}H_{16}ClNO_3$ (341.80)	66.77 (66.81)	4.72 (4.65)	4.10 (4.22)
6g	211-213	56		$C_{17}H_{13}BrClNO$ (362.66)	56.30 (56.21)	3.61 (3.78)	3.86 (4.01)

indole ketone **7** arising from the recyclisation of one of the furan rings [18b] with subsequent cyclization on the β-position of the second furan.

also by condensation of 2-methylfuran with corresponding 2-acetylaminobenzaldehydes in the presence of an acidic catalyst. We supposed that the conditions of the

Scheme 3



5 a-g **6 a-g** **4 a-g**

Table 3

H^1 NMR Data of Compounds **5**, **6**

Comp.	^{1}H NMR (ppm, $CDCl_3$)	Comp.	^{1}H NMR (ppm, CF_3COOD)
5a	2.02 (s, 3H, CH_3), 2.26 (s, 6H, CH_3), 5.42 (s, 1H, CH), 5.92 (d, *J* = 3.2 Hz, 2H, H_{Fur}), 5.95 (d, *J* = 3.2 Hz, 2H, H_{Fur}), 7.11-7.14 (m, 1H, H_{Ar}), 7.25-7.33 (m, 2H, H_{Ar}), 7.42 (s, 1H, NH), 7.82-7.85 (m, 1H, H_{Ar})	**6a**	2.98 (s, 3H, CH_3); 3.22 (s, 3H, CH_3); 7.30 (s, 1H, H_{Fur}); 7.78-7.85 (m, 1H, H_{Ar}); 8.48 (d, *J* = 11.0 Hz, 1H, H_{Trop}); 8.90 (d, *J* = 11.0 Hz, 1H, H_{Trop}); 9.03-9.07 (m, 1H, H_{Ar})
5b	2.02 (s, 3H, CH_3), 2.26 (s, 6H, CH_3), 3.79 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 5.34 (s, 1H, CH), 5.92 (d, *J* = 3.2 Hz, 2H, H_{Fur}), 5.94 (d, *J* = 3.2 Hz, 2H, H_{Fur}), 6.64 (s, 1H, H_{Ar}), 7.28 (s, 1H, NH), 7.39 (s, 1H, H_{Ar})	**6b**	2.95 (s, 3H, CH_3); 3.18 (s, 3H, CH_3); 4.21 (s, 3H, OCH_3); 4.26 (s, 3H, OCH_3); 7.28 (s, 1H, H_{Fur}); 7.49 (s, 1H, H_{Ar}); 8.34 (d, *J* = 11.0 Hz, 1H, H_{Trop}); 8.49 (s, 1H, H_{Ar}); 8.78 (d, *J* = 11.0 Hz, 1H, H_{Trop})
5c	1.20 (t, *J* = 7.5 Hz, 6H, CH_3), 2.01 (s, 3H, CH_3), 2.61 (q, *J* = 7.5 Hz, 4H, CH_2), 3.78 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 5.36 (s, 1H, CH), 5.92-5.96 (m, 4H, H_{Fur}), 6.62 (s, 1H, H_{Ar}), 7.29 (s, 1H, NH), 7.40 (s, 1H, H_{Ar})	**6c**	1.62 (t, *J* = 7.6 Hz, 3H, CH_3); 1.72 (t, *J* = 7.6 Hz, 3H, CH_3); 3.33 (q, *J* = 7.6 Hz, 2H, CH_2); 3.51 (q, *J* = 7.6 Hz, 2H, CH_2); 4.23 (s, 3H, OCH_3); 4.27 (s, 3H, OCH_3); 7.33 (s, 1H, H_{Fur}); 7.50 (s, 1H, H_{Ar}); 8.38 (d, *J* = 11.0 Hz, 1H, H_{Trop}); 8.50 (s, 1H, H_{Ar}); 8.82 (d, *J* = 11.0 Hz, 1H, H_{Trop})
5d	2.03 (s, 3H, CH_3), 2.26 (s, 6H, CH_3), 5.33 (s, 1H, CH), 5.91 (d, *J* = 3.2 Hz, 2H, H_{Fur}), 5.93 (d, *J* = 3.2 Hz, 2H, H_{Fur}), 6.59 (s, 1H, H_{Ar}), 7.16 (s, 1H, NH), 7.22 (s, 1H, H_{Ar})	**6d**	2.94 (s, 3H, CH_3); 3.16 (s, 3H, CH_3); 6.29 (s, 2H, CH_2); 7.24 (s, 1H, H_{Fur}); 7.34 (s, 1H, H_{Ar}); 8.30 (d, *J* = 11.0 Hz, 1H, H_{Trop}); 8.31 (s, 1H, H_{Ar}); 8.69 (d, *J* = 11.0 Hz, 1H, H_{Trop})
5e	1.20 (t, *J* = 7.5 Hz, 6H, CH_3), 2.02 (s, 3H, CH_3), 2.61 (q, *J* = 7.5 Hz, 4H, CH_2), 5.34 (s, 1H, CH), 5.93 (s, 4H, H_{Fur}), 6.58 (s, 1H, H_{Ar}), 7.20 (s, 1H, NH), 7.23 (s, 1H, H_{Ar})	**6e**	1.60 (t, *J* = 7.6 Hz, 3H, CH_3); 1.68 (t, *J* = 7.6 Hz, 3H, CH_3); 3.32 (q, *J* = 7.6 Hz, 2H, CH_2); 3.48 (q, *J* = 7.6 Hz, 2H, CH_2); 6.28 (s, 2H, CH_2); 7.28 (s, 1H, H_{Fur}); 7.35 (s, 1H, H_{Ar}); 8.31 (s, 1H, H_{Ar}); 8.33 (d, *J* = 11.0 Hz, 1H, H_{Trop}); 8.78 (d, *J* = 11.0 Hz, 1H, H_{Trop})
5f	2.00 (s, 3H, CH_3), 2.25 (s, 6H, CH_3), 4.22 (s, 4H, CH_2CH_2), 5.30 (s, 1H, CH), 5.90 (d, *J* = 3.2 Hz, 2H, H_{Fur}), 5.93 (d, *J* = 3.2 Hz, 2H, H_{Fur}), 6.63 (s, 1H, H_{Ar}), 7.15 (s, 1H, NH), 7.27 (s, 1H, H_{Ar})	**6f**	2.94 (s, 3H, CH_3); 3.16 (s, 3H, CH_3); 4.54-4.58 (m, 4H, CH_2CH_2); 7.22 (s, 1H, H_{Fur}); 7.41 (s, 1H, H_{Ar}); 8.33 (d, *J* = 11.0 Hz, 1H, H_{Trop}); 8.47 (s, 1H, H_{Ar}); 8.66 (d, *J* = 11.0 Hz, 1H, H_{Trop})
5g	2.01 (s, 3H, CH_3), 2.26 (s, 6H, CH_3), 5.37 (s, 1H, CH), 5.93 (d, *J* = 3.1 Hz, 2H, H_{Fur}), 5.97 (d, *J* = 3.1 Hz, 2H, H_{Fur}), 6.99 (d, *J* = 8.1 Hz, 1H, H_{Ar}), 7.24 (d, *J* = 8.1 Hz, 1H, H_{Ar}), 7.44 (br s, 1H, NH), 8.12 (s, 1H, H_{Ar})	**6g**	2.97 (s, 3H, CH_3); 3.23 (s, 3H, CH_3); 7.33 (s, 1H, H_{Fur}); 7.93 (d, *J* = 8.7 Hz, 1H, H_{Ar}); 8.16 (s, 1H, H_{Ar}); 8.53 (d, *J* = 11.0 Hz, 1H, H_{Trop}); 8.88 (d, *J* = 8.7 Hz, 1H, H_{Ar}); 8.90 (d, *J* = 11.0 Hz, 1H, H_{Trop})

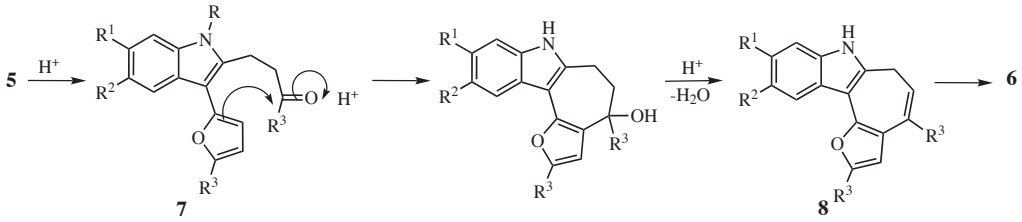
Disproportionation of the resulted cycloheptatriene **8** under the action of the excess of hydrogen chloride accomplishes the formation of chlorides **6** (Scheme 4). A similar transformation was observed earlier under the treatment of 2-hydroxybenzylfurans with excess of perchloric acid [20]

2-Acetylaminobenzylfurans **5**, which are starting compounds for preparation of the salts **6**, can be prepared

recyclization (gaseous hydrogen chloride/methanol) are suitable for the preparation of the salts **6** directly from the aldehydes **11** and 2-methylfuran without the isolation of the intermediate compounds **5**. For this purpose we synthesized *o*-acetylaminobenzaldehydes **11** (Scheme 5).

In fact, under the passing of gaseous hydrogen chloride through methanolic solutions of the aldehydes **11** and 2-

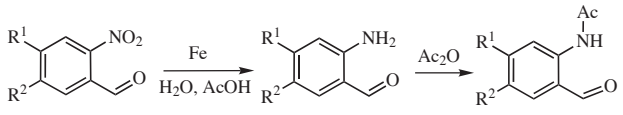
Scheme 4



R = Ac or H

methylfuran the tetracyclic salts **6** (method B) (Scheme 6) were isolated as main products. At the same time all attempts to obtain such salts directly from aminobenzaldehydes **10** and 2-methylfuran failed.

Scheme 5

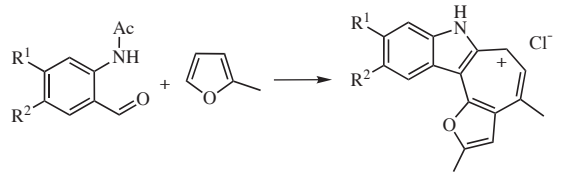


9 a-c **10 a-c** **11 a-c**

9, 10, 11	**a**	**b**	**c**
$R^1 = R^2$	OMe	OCH_2O	OCH_2CH_2O

Thus we elaborated the methods of the synthesis of the tetracyclic salts containing indole fragment and pharmaceutically acceptable counter-ion. The new method that allows the preparation of the condensed tetracyclic salts directly from 2-acetylaminobenzaldehydes and 2-methylfuran is proposed.

Scheme 6



11 a-c **6 b,d,f**

EXPERIMENTAL

^{1}H NMR spectra were recorded in $CDCl_3$ and in CF_3COOD on a Bruker AC 200 spectrometer at 200 MHz. Chemical shifts are reported in ppm relative to tetramethylsilane as an internal standard. IR spectra were recorded on InfraLUM FT-02. Melting points are uncorrected.

2-Nitro-4-bromophenylbis(5-methyl-2-furyl)methane (**3g**).

To a solution of 2-nitro-4-bromobenzaldehyde (11.5 g, 50 mmol) and 2-methylfuran (15 mL, 167 mmol) in dioxane (50 mL) perchloric acid (1 mL) was added. The reaction mixture was maintained at 70–75°C until the reaction was completed (TLC control). The reaction mixture was poured into water (500 mL) and left overnight. The precipitated product was collected by filtration, washed with water. A recrystallization from ethanol gave 11.35 g (60%) of **3g** as yellow-green crystals, mp 80-81°C (ethanol). ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.25 (s, 6H, CH_3), 5.90 (d, J = 3.1 Hz, 2H, 4-H_{Fur}), 5.95 (d, J = 3.1 Hz, 2H, 3-H_{Fur}), 6.15 (s, 1H, CH), 7.26 (d, J = 8.4 Hz, 1H, H_{Ar}), 7.65 (d.d, J = 2.1, 8.4 Hz, 1H, H_{Ar}), 8.08 ppm (d, J = 2.1 Hz, 1H, H_{Ar}).

Anal. Calcd. for $C_{17}H_{14}BrNO_4$ (376.21): C, 54.28; H, 3.75; N, 3.72. Found: C, 53.98; H, 3.93; N, 3.89.

Compounds **3a-f** were obtained analogously, and physical data are in accordance with those reported earlier [21].

General Procedure for the Synthesis of 2-Aminoaryldifurylmethanes **4**.

A mixture of compound **3** (6 mmol), Raney Ni (1.5 g), ethanol (20 mL) and hydrazine-hydrate (2 mL) was refluxed until the completion of the reduction (TLC control). The nickel was filtered off and the filtrate was evaporated to dryness. Obtained amines **4** were used at the next step without further purification.

General Procedure for the Synthesis of 2-Acetylaminoaryldifurylmethanes **5**.

A mixture of 2-aminoaryldifurylmethane **4** (15 mmol) and acetic anhydride (30 mmol) was left at 35-40°C for 20-25 min until full consumption of the starting compound **4** was observed (TLC control). The reaction mixture was poured into water (400 mL) and left overnight. The separated product was collected by filtration and recrystallized from CH_2Cl_2/hexane mixture.

2-Acetylamino-4-bromophenylbis(5-methylfur-2-yl)-methane (**5g**) was obtained according to the general method except the reaction mixture was kept at 20-25°C.

General Procedure for the Synthesis of Furo[2',3':3,4]cyclohepta[1,2-*b*]indolium Chlorides **6** (method A).

Compound **5** (10 mmol) was dissolved in methanol (50 mL) at 50-55°C and gaseous hydrogen chloride was passed through the solution until the precipitation of crystalline compound was completed (~ 70-80 min). The reaction mixture was left for 10 hours at room temperature; the solid was collected by filtration and washed with small amount of ether.

Analogously furo[2',3':3,4]cyclohepta[1,2-*b*]indolium chlorides **6** were obtained by passing the hydrogen chloride through methanolic solution of the compounds **4**.

General Procedure for the Synthesis of 2-Aminobenzaldehydes **10**.

A mixture of 2-nitrobenzaldehyde **9** (24 mmol), iron powder (15 g), ethylacetate (14 mL), water (180 mL) and glacial acetic acid (5 ml) was brought up carefully to reflux under vigorous stirring and was allowed to boil for additional 20-30 minutes. After the reduction was completed (TLC control), the mixture

was neutralized with $NaHCO_3$ (40 g) and the solid was filtered off. The organic layer was separated, and the water layer was extracted with ethylacetate (3 × 20 mL). The combined organic extract was purified with active charcoal and evaporated to dryness. The aminobenzaldehyde obtained was used at the next step without further purification.

2-Amino-4,5-methylenedioxybenzaldehyde (**10b**).

This compound was obtained from 2-nitro-4,5-methylenedioxybenzaldehyde (**9b**) according to the general method in 72% yield as dark-yellow crystals, mp 104-105°C. ^{1}H NMR (300 MHz, $CDCl_3$), δ 5.92 (s, 2H, CH_2); 6.14 (s, 1H, H_{Ar}); 6.27 (br s, 2H, NH_2); 6.82 (s, 1H, H_{Ar}); 9.61 ppm (s, 1H, CHO).

Anal. Calcd. for $C_8H_7NO_3$ (165.15): C, 58.18; H, 4.27; N, 8.48. Found: C, 58.31; H, 4.36; N, 8.62.

General Procedure for the Synthesis of 2-Acetylaminobenzaldehydes **11**.

The mixture of 2-aminobenzaldehyde **10** (10 mmol) and acetic anhydride (30 mmol) was kept at 55-60°C for 10-15 min (TLC control). The reaction mixture was poured into water (300 mL) and left overnight at room temperature. The precipitate was collected by filtration, washed with water and recrystallized from ethanol.

2-Acetylamino-4,5-dimethoxybenzaldehyde (**11a**).

This compound was obtained from the 2-amino-4,5-dimethoxybenzaldehyde (**10a**) according to the general method in 61% yield as yellow crystals, mp 169-170°C. ^{1}H NMR (200 MHz, $CDCl_3$), δ 2.23 (s, 3H, CH_3); 3.91 (s, 3H, OCH_3); 3.98 (s, 3H, OCH_3); 7.03 (s, 1H, H_{Ar}); 8.47 (s, 1H, H_{Ar}); 9.75 (s, 1H, CHO); 11.31 ppm (br s, 1H, NH).

Anal. Calcd. for $C_{11}H_{13}NO_4$ (223.23): C, 59.19; H, 5.87; N, 6.27. Found: C, 59.23; H, 5.96; N, 6.41.

2-Acetylamino-4,5-methylenedioxybenzaldehyde (**11b**).

This compound was obtained from 2-amino-4,5-methylenedioxybenzaldehyde (**10b**) according to the general method in 68% yield as yellow crystals, mp 164-165°C. 1H NMR (200 MHz, CDCl3), δ 2.22 (s, 3H, CH3); 6.05 (s, 2H, CH2); 6.99 (s, 1H, HAr); 8.34 (s, 1H, HAr); 9.67 (s, 1H, CHO); 11.44 ppm (br. s, 1H, NH).

Anal. Calcd. for $C_{10}H_9NO_4$ (207.19): C, 57.97; H, 4.38; N, 6.76. Found: C, 58.09; H, 4.45; N, 6.84.

2-(Acetylamino)-4,5-ethylenedioxybenzaldehyde (**11c**).

This compound was obtained from the 2-amino-4,5-ethylenedioxybenzaldehyde (**10c**) according to the general method in 63% yield as yellow crystals, mp 142-143°C. ^{1}H NMR (200 MHz, $CDCl_3$), δ 2.20 (s, 3H, CH_3); 4.25-4.27 (m, 2H, CH_2); 4.33-4.35 (m, 2H, CH_2); 7.11 (s, 1H, H_{Ar}); 8.27 (s, 1H, H_{Ar}); 9.68 (s, 1H, CHO); 11.02 ppm (br. s, 1H, NH).

Anal. Calcd. for $C_{11}H_{11}NO_4$ (221.21): C, 59.73; H, 5.01; N, 6.33. Found: C, 59.87; H, 5.11; N, 6.47.

General Procedure for the Synthesis of Furo[2',3':3,4]cyclohepta-[1,2-*b*]indolium Chlorides **6** (method B).

Gaseous hydrogen chloride was passed through the hot solution of the compound **11** (4.5 mmol) in methanol (20 mL) for 50-60 min. The reaction mixture maintained for 2 hours at room temperature. The precipitated compound **6** was collected by filtration and washed with a small amount of ether.

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