New quinoline- and isoquinoline-based multicomponent methods for the synthesis of 1,1(3,3)-dicyanotetrahydrobenzoindolizines

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Convenient multicomponent methods for the synthesis of benzannulated dihydroindolizines based on quinoline or isoquinoline, malononitrile, aromatic aldehydes and α-halomethylcarbonyl compounds were developed. Several alternative protocols of using the reactants were studied, starting with separate generation of two most probable intermediates and ending with the four-component condensation of all reactants. The scope of applicability of these methods was found, depending on the initial compounds used. The reaction is highly stereoselective with predominant formation of one of the possible isomers.

Key words: tetrahydroindolizines, quinoline, isoquinoline, cycloaddition, multicomponent synthesis, stereoselective.

The reactions of azinium ylides with alkenes activated by an electron-withdrawing substituent present in the molecule afford carbo- and heterocyclic systems.[1—4] The reactions of pyridinium ylides with 1,1-dicyanoethylenes give cyclopropane derivatives.[5,6] Meanwhile, the addition of π-deficient pyridinium, isoquinolinium, and quinolinium ylides to 1,1-dicyanoethylenes results in the formation of hydrogenated indolizines.[1—5,7,8] Previously, we developed a convenient method for the synthesis of 1,1-dicyanotetrahydroindolizines based on isoquinolinium ylides, and also 3-cyano-, 3-ethoxycarbonylpyridinium ylides and 1,1-dicyanoethylenes.[5,7,9,10]

Recently, a similar synthetic method based on quinolinium ylides has been reported.[8] Relatively recently, polyfunctional tetrahydroindolizines have been found to exhibit biological activity, in particular, antimycotic and antibacterial activities.[11] The cycloadducts based on isoquinolinium and quinolinium ylides are efficient protein arginine deiminase and malarial (*P. Falciparum*) cysteine protease inhibitors [12,13] and also inhibit the migration of pancreatic cancer cells.[14]

Owing to the enhanced interest in these compounds, an obvious goal is to study new simplified and efficient synthetic routes to hydrogenated indolizines. One of such options is the multicomponent process that eliminates the necessity of preliminary synthesis of the starting nitriles, some of which are evident lachrymators.[15] There is also no need to isolate pure quaternary azinium salts, which are often hygroscopic.

Results and Discussion

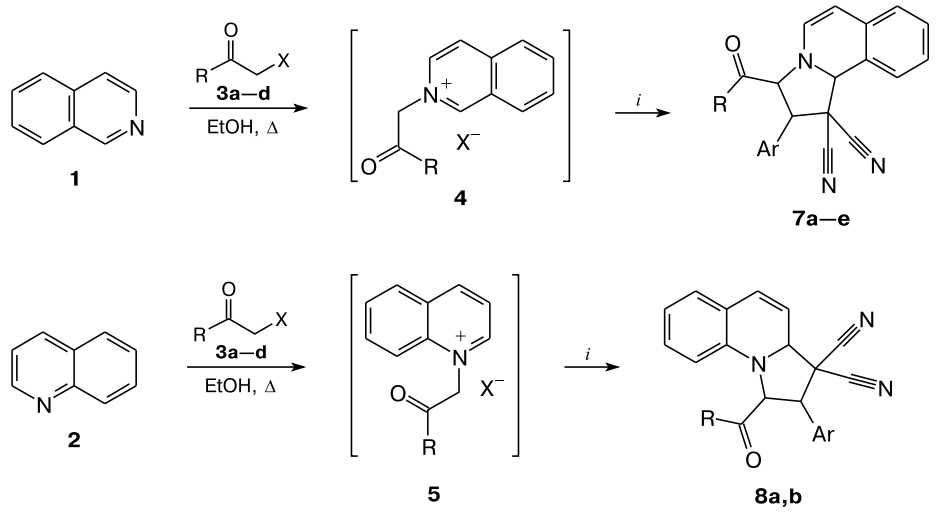
In this study, we addressed several multicomponent methods for the synthesis of tetrahydroindolizines. As the starting compounds, we chose isoquinoline (**1**), quinoline (**2**), phenacyl bromide (**3**), malononitrile, and unsubstituted benzaldehyde (**6**) (Scheme 1). Compounds **7a** and **8a** were prepared by methods ***A—C***.

The data on the yields of target tetrahydroindolizines **7a** and **8a** are summarized in Table 1.

In the initial, four-component version (see Table 1, entry *1*, method ***A***), an ethanol solution of all reactants, that is, quinoline or isoquinoline, phenacyl bromide, benzaldehyde, and malononitrile, was heated at reflux, then triethyamine was added, and the mixture was stirred at room temperature. The sequence of reactions that proceeded in the system included quaternization of azine, ylide generation, Knoevenagel condensation of benzaldehyde with malononitrile, and the cyclocondensation of the intermediate compounds, resulting in the formation of indolizines. However, this protocol gives a rather low yield of tetrahydroindolizines when phenacyl bromide (**3a**) is used as the halogenating agent, while in the case of 1-(bromoacetyl)adamantane (**3b**) (see Scheme 1) and

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 2, pp. 0297—0303, February, 2018.
1066-5285/18/6702-0297

Scheme 1



3: X = Br, R = Ph (**a**), 1-Ad (**b**), Me (**c**); X = Cl, R = Me (**d**)
6: Ar = Ph (**a**), 3-Br-4-MeOC_6H_3 (**b**), 2,5-$(OMe)_2C_6H_3$ (**c**), 3,4,5-$(OMe)_3C_6H_2$ (**d**)

i. $CH_2(CN)_2$, ArCHO (**6a—d**), Et_3N, 20 °C

Compound	R	Ar
7a	Ph	Ph
7b	1-Ad	Ph
7c	1-Ad	3-Br-4-MeOC_6H_3

Compound	R	A r
7d	1-Ad	2,5-$(OMe)_2C_6H_3$
7e	1-Ad	3,4,5-$(OMe)_3C_6H_2$
8a	Ph	Ph
8b	1-Ad	Ph

Table 1. Dependence of the yields of tetrahydroindolizines **7a** and **8a** on the conditions of multicomponent synthesis

Entry	Method	Yield (%)	
		7a	**8a**
1	***A***	49	27
2	***B***	68	44
3	***C***	80	59
4	***L***[a]	98[7]	68[b]

[a] ***L*** is a method reported in the literature.
[b] Since compound **8a** has not been reported, the yield is given for its 2-(4-methoxyphenyl) analogue. [8]

Table 2. Yields of adamantane tetrahydroindolizines **7b—e** and **8b** prepared by method ***C***

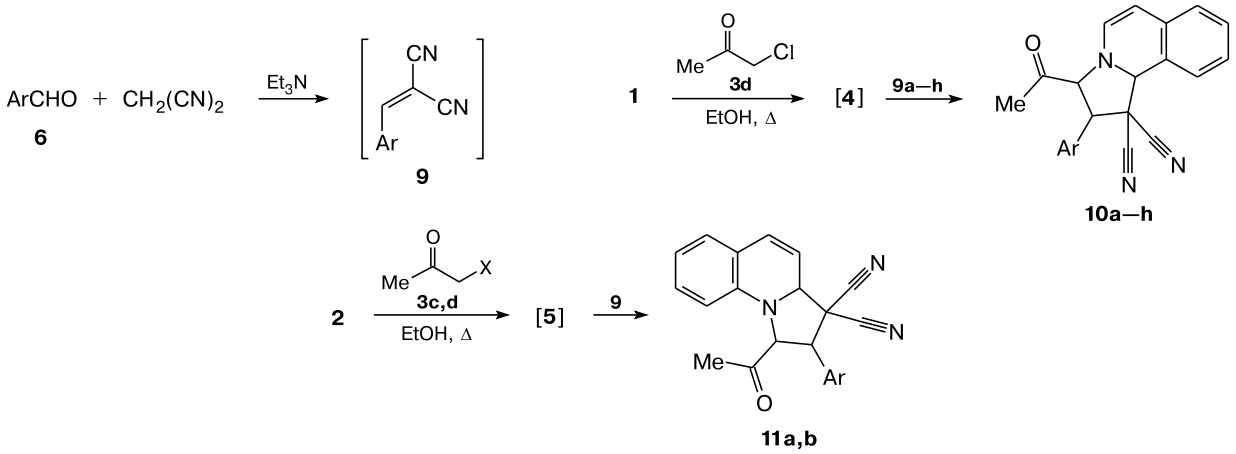
Entry	Compound	Yield (%)
1	**7b**	57
2	**7c**	66
3	**7d**	72
4	**7e**	38
5	**8b**	31

bromo- (**3c**) and chloroacetone (**3d**), the target adducts cannot be isolated. The low yields may be attributable to the competing side reactions such as alkylation of malononitrile with haloketone and condensation involving the aldehyde and the methylene-active bromo- and chloroacetone.

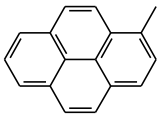
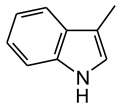
Subsequently, the quaternary salt was initially generated by heating an ethanol solution of **1** or **2** with haloketone, and then benzaldehyde, malononitrile, and triethylamine were added to the reaction mixture (method ***B***, see Table 1, entry *2*). The condensation with preliminary generation of the azinium salt *in situ* increases the yield of adducts **7a** and **8a** by a factor of 1.5 with respect to that in method ***A***. Using this method, a number of isoquinoline and quinoline adducts based on azines quaternized with 1-(bromoacetyl)adamantane and various arenecarbaldehydes were prepared in moderate yields (see Table 2, entries *1—5*).

According to method ***C***, the quaternization step was excluded. A ready-prepared azinium salt was used; it was mixed with benzaldehyde and malononitrile in ethanol. The addition of triethylamine resulted in the ylide generation and Knoevenagel condensation proceeding simultaneously (see Table 1, entry *3*). The yields of the target tetrahydroindolizines **7a** and **8a** were close to the yields of compounds obtained in the two-component process (see Table 1, entry *4*), when benzylidenemalononitrile reacts with the ylide generated from the ready azinium salt **4** or **5** (see Scheme 1). Method ***C*** can be

Scheme 2



X = Br (**3c**), Cl (**3d**)

Compound	Ar	Compound	Ar	Compound	Ar
9a, **10a**, **11a**	Ph				
9b, **10b**, **11b**	4-MeC_6H_4				
9c, 10c	4-$MeOC(O)C_6H_4$	**9g**, **10g**		**9h**, **10h**	
9d, 10d	3-Br-4-$MeOC_6H_3$				
9e, **10e**	2,5-$(OMe)_2C_6H_3$				
9f, **10f**	3,4,5-$(OMe)_3C_6H_2$				

used to prepare adamantane derivatives **7b** and **8b** (Table 2); however, the preparation and application of the *N*-acetonylquinolinium and *N*-acetonylisoquinolinium salts is often difficult, because they are hygroscopic (especially chlorides).

Acetyl derivatives were prepared (see Scheme **2**) using actually a two-component condensation without isolation of the intermediate salts of quaternized azines **4**, **5** and arylidenemalononitriles **9** (method ***D***). Solutions of compounds **4**, **5**, and **9** were formed separately and then mixed. This gave a series of acetyl tetrahydroindolizine derivatives (Table 3, entries *1—9*, *11*).

Note that the reactivities of bromo- and chloroacetones are different. In the case of tetrahydroindolizines **10** based on isoquinoline, the use of chloroacetone according to method ***D*** is only possible (see Table 3, entries *1—8*). Quinoline derivatives **11a**,**b** were obtained by method ***D*** (see Table 3, entries *9*, *11*). Adduct **11a** was also successfully synthesized by method ***B*** with preliminary generation of the azinium salt from bromoacetone and quinoline (see Table 3, entry *10*). The replacement of bromoacetone by chloroacetone in a similar multicomponent process does not give the desired tetrahydroindolizine **11a**.

It is known that cyclocondensations involving azinium ylides are highly regioselective and highly stereoselective.[1,7—9,16] The regioselectivity of these reactions is attributable to the orientation of the charged ylide and 1,1-dicyanooethylene caused by dipole—dipole interactions.[7] Unlike the reactions of pyridinium ylides with

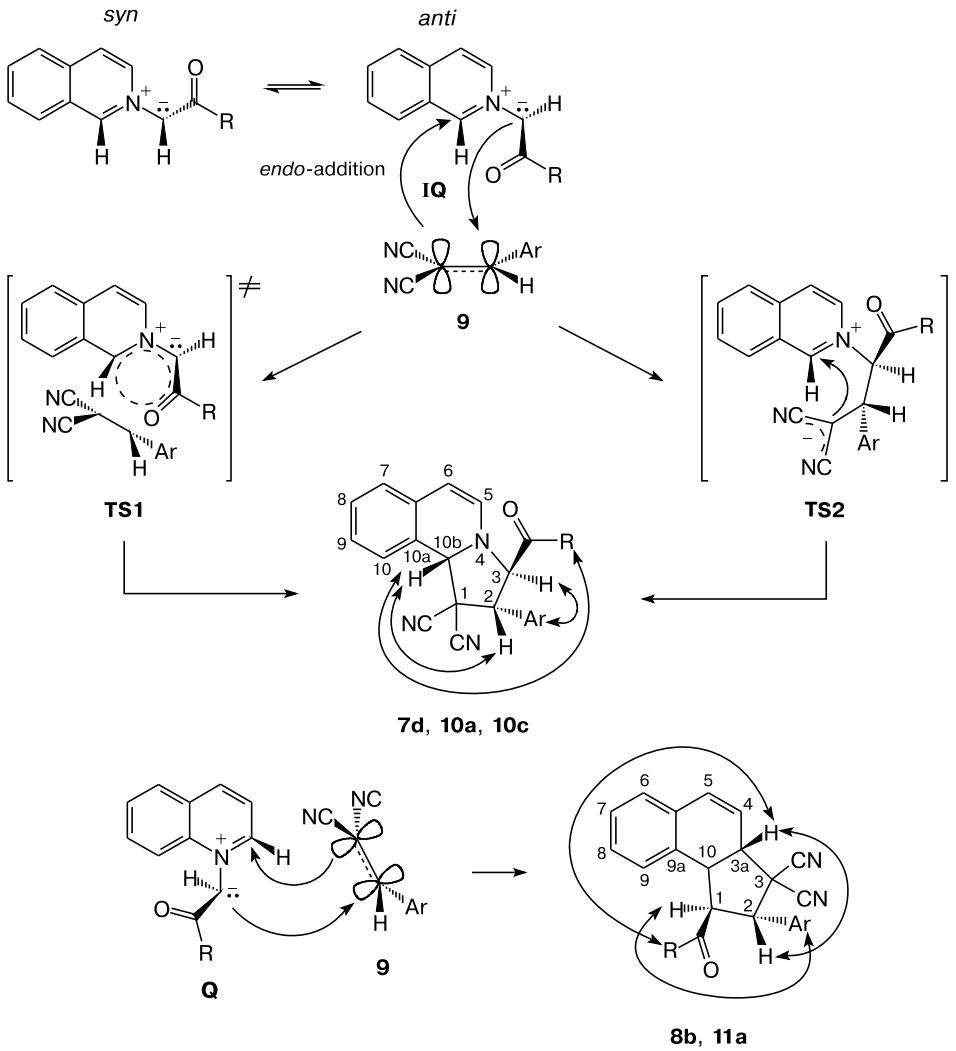
Table 3. Yields of acetyl tetrahydroindolizine derivatives **10a—h** and **11a—b** prepared by method ***D***

Entry	Compound	Yield (%)
1	**10a**	55
2	**10b**	70
3	**10c**	71
4	**10d**	62
5	**10e**	71
6	**10f**	34
7	**10g**	61
8	**10h**	52
9	**11a**	31
10	**11a***	43
11	**11b**	62

* Obtained by method ***B***.

arylidenemalononitriles **9**, which follow the Ad_N-E mechanism and give rise to cyclopropane derivatives, the reactions of π-deficient isoquinolinium and quinolinium ylides with compounds **9** can be interpreted in two ways. They can be described either as synchronous 1,3-dipolar *endo*-cycloaddition,[1] which proceeds *via* transition state **TS1** in the case of isoquinoline derivatives (Scheme 3), or as a sequence of *endo*-addition and nucleophilic attack at the α-position of azine[8] (**TS2**). Regardless the mechanism of this reaction, its stereochemical outcome for isoquinolinium (**IQ**) and quinolinium (**Q**) ylides is the same; only one of several diastereomeric adducts is formed.

Scheme 3



High stereoselectivity of formation of the cycloadducts implies that the *anti*-form of the **IQ** and **Q** azinium ylides predominantly participates in the reaction. The **IQ** and **Q** ylides have *endo*-orientation relative to the aryl substituent of arylidenemalononitrile **9**. The data of 2D NOESY ^{1}H NMR spectroscopy of the series of benzannulated tetrahydroindolizines **7d**, **8b**, **10a**, **10c**, and **11a** we obtained confirm the predominant formation of one of diastereomers as a result of *endo*-addition of the *anti*-form of isoquinolinium **IQ** and quinolinium **Q** ylides.

Experimental

One-dimensional NMR spectra were measured on a Bruker AM 300 spectrometer (^{1}H, 300.13 and ^{13}C, 75.47 MHz, DMSO-d_6, $SiMe_4$ as the internal standard.) The 2D NMR spectra for COSY and NOESY experiments were recorded on a Bruker Avance 600 spectrometer (^{1}H, 600.13 MHz) at 25 °C in DMSO-d_6 using $SiMe_4$ as the internal standard. The atom numbering in the NMR spectra of the target products corresponds to the numbering presented in Scheme 3 and to the IUPAC nomenclature. Melting points were determined on an EZ Melt apparatus, Stanford research systems, USA. The synthesis of quaternary salts **4** and **5** was described previously.[8]

Four-component synthesis of benzannulated tetrahydroindolizines (method *A*). A flask equipped with a magnetic stirrer was charged successively with ethanol (7 mL), isoquinoline or quinoline (3.0 mmol), phenacyl bromide (3.0 mmol), benzaldehyde (3.0 mmol), and malononitrile (3.0 mmol). The reaction mixture was refluxed with stirring for 1.5 h and cooled. At room temperature, triethylamine (3.3 mmol) was added, and the mixture was stirred for 2.5 h. The precipitate that formed was collected on a filter and washed successively with water (15 mL), ethanol (5 mL), and hexane (5 mL).

Synthesis of benzannulated tetrahydroindolizines with preliminary generation of quaternary salt (method *B*). A flask was charged successively with ethanol (7 mL), isoquinoline or quinoline (3.0 mmol), and bromoketone (3.0 mmol). The reaction mixture was refluxed with stirring for 1.5 h and cooled.

At room temperature, aromatic aldehyde (3.0 mmol) and malononitrile (3.0 mmol) were added, and the mixture was kept for 2.5 h. The workup was similar to that described for method ***A***.

Three-component synthesis of benzannulated tetrahydroindolizines (method *C*). A flask was charged successively with ethanol (7 mL), and azinium salt (3.0 mmol), aromatic aldehyde (3.0 mmol), and malononitrile (3.0 mmol) were added with stirring. At room temperature, triethylamine (3.3 mmol) was added, and the mixture was stirred for 2.5 h. The workup was similar to that described for method ***A***.

3-Benzoyl-2-phenyl-2,3-dihydropyrrolo[2,1-*a*]isoquinoline-1,1(10b*H*)-dicarbonitrile (7a). Syntheses by methods ***A***, ***B***, and ***C*** gave 0.59 g (49%), 0.81 g (68%), and 0.96 g (80%) of the target product, respectively, m.p. 145—147 °C (*cf.* lit.[7]: 122—123 °C). ^{1}H NMR (DMSO-d_6), δ: 4.62 (d, 1 H, H(2), J = 7.0 Hz); 5.47 (d, 1 H, H(6), J = 7.7 Hz); 5.58 (s, 1 H, H(10b)); 6.07 (d, 1 H, H(3), J = 7.0 Hz); 6.87 (d, 1 H, H(5), J = 7.7 Hz); 7.12 (d, 1 H, H(7), J = 7.7 Hz); 7.21 (m, 1 H, H(9)); 7.33 (m, 2 H, H(8), H(10)); 7.41—7.51 (m, 5 H, Ar); 7.62 (m, 3 H, Ar); 7.91 (d, 2 H, Ar, J = 7.7 Hz). ^{13}C NMR (DMSO-d_6), δ: 50.1, 52.5, 68.9, 69.8, 99.4, 113.6, 123.2, 124.8, 126.0, 126.4, 128.5, 128.8, 128.9, 129.0, 129.2, 129.9, 132.5, 133.6, 133.7, 134.7, 134.9, 195.3.

1-Benzoyl-2-phenyl-1,2-dihydropyrrolo[1,2-*a*]quinoline-3,3(3a*H*)-dicarbonitrile (8a). Syntheses by methods ***A***, ***B***, and ***C*** gave 0.33 g (27%), 0.53 g (44%), and 0.71 r (59%) of the target product, respectively, m.p. 167—169 °C. ^{1}H NMR (DMSO-d_6) δ: 4.38 (d, 1 H, H(2), J = 8.1 Hz); 5.71 (m, 1 H, H(3a)); 5.94 (dd, 1 H, H(4), J = 10.2 Hz, J = 2.2 Hz); 6.07 (d, 1 H, H(1), J = 8.1 Hz); 6.11 (d, 1 H, H(9), J = 7.9 Hz); 6.67 (m, 1 H, H(7)); 6.81 (d, 1 H, H(5), J = 10.2 Hz); 7.00 (m, 1 H, H(8)); 7.06 (d, 1 H, H(6), J = 7.0 Hz); 7.33 (m, 2 H, Ar); 7.44 (m, 3 H, Ar); 7.62 (m, 3 H, Ar); 7.80 (d, 2 H, Ar, J = 7.5 Hz). ^{13}C NMR (DMSO-d_6), δ: 48.7, 54.2, 63.5, 68.9, 110.3, 112.5, 116.1, 118.3, 119.0, 127.7, 128.5, 128.8, 128.9, 129.0, 129.4, 129.9, 130.2, 132.3, 134.1, 134.6, 140.7, 196.6. Found (%): C, 80.74; H, 4.76; N, 10.39. $C_{27}H_{19}N_3O$. Calculated (%): C, 80.78; H, 4.77; N, 10.47.

Tetrahydroindolizines **7b—e**, **8b** were synthesized by method ***B***.

3-(Adamantane-1-carbonyl)-2-phenyl-2,3-dihydropyrrolo-[2,1-*a*]isoquinoline-1,1(10b*H*)-dicarbonitrile (7b). Product yield 0.79 g (57%), m.p. 151—152 °C. ^{1}H NMR (DMSO-d_6), δ: 1.53—1.70 (m, 12 H, Ad); 1.87 (m, 3 H, Ad); 4.35 (d, 1 H, H(2), J = 6.2 Hz); 5.42 (d, 1 H, H(3), J = 6.2 Hz); 5.45 (d, 1 H, H(6), J = 7.7 Hz); 5.58 (s, 1 H, H(10b)); 6.76 (d, 1 H, H(5), J = 7.7 Hz); 7.12 (d, 1 H, H(7), J = 7.4 Hz); 7.20 (m, 1 H, H(9)); 7.32 (m, 1 H, H(8)); 7.36 (d, 1 H, H(10), J = 7.5 Hz); 7.45 (m, 3 H, Ar); 7.64 (d, 2 H, Ar, J = 7.4 Hz). ^{13}C NMR (DMSO-d_6), δ: 27.0, 35.6, 36.3, 45.9, 49.8, 53.7, 67.2, 69.7, 99.5, 113.6, 123.1, 124.8, 126.0, 126.4, 128.5, 128.9, 129.2, 129.9, 132.4, 133.5, 134.9, 211.3. Found (%): C, 80.79; H, 6.14; N, 8.99. $C_{31}H_{29}N_3O$. Calculated (%): C, 81.02; H, 6.36; N, 9.14.

3-(Adamantane-1-carbonyl)-2-(3-bromo-4-methoxyphenyl)-2,3-dihydropyrrolo[2,1-*a*]isoquinoline-1,1(10b*H*)-dicarbonitrile (7c). The product was isolated in 1.12 g (66%) yield, m.p. 162—164 °C. ^{1}H NMR (DMSO-d_6), δ: 1.63—1.73 (m, 12 H, Ad); 1.93 (m, 3 H, Ad); 3.89 (s, 3 H, CH_3); 4.36 (d, 1 H, H(2), J = 6.2 Hz); 5.43—5.47 (m, 2 H, H(3), H(6)); 5.56 (s, 1 H, H(10b)); 6.76 (d, 1 H, H(5), J = 7.7 Hz); 7.12 (d, 1 H, H(7), J = 7.7 Hz); 7.21 (m, 2 H, H(9), Ar); 7.36 (m, 2 H, H(8), H(10)); 7.66 (d, 1 H, Ar, J = 8.4 Hz); 7.90 (s, 1 H, Ar). ^{13}C NMR (DMSO-d_6), δ: 27.1, 35.6, 36.0, 46.3, 46.7, 49.4, 56.3, 67.1, 69.7, 100.1, 110.7, 112.6, 113.2, 124.1, 124.9, 126.5, 127.0, 127.3, 129.9, 130.3, 130.5, 132.6, 133.0, 155.9, 204.2. Found (%): C, 67.60; H, 5.39; N, 7.34. $C_{32}H_{30}BrN_3O_2$. Calculated (%): C, 67.61; H, 5.32; N, 7.39.

3-(Adamantane-1-carbonyl)-2-(2,5-dimethoxyphenyl)-2,3-dihydropyrrolo[2,1-*a*]isoquinoline-1,1(10b*H*)-dicarbonitrile (7d). The product yield was 1.13 g (72%) , m.p. 168—170 °C. ^{1}H NMR (DMSO-d_6), δ: 1.64—1.78 (m, 12 H, Ad); 1.95 (m, 3 H, Ad); 3.76 (s, 3 H, CH_3); 3.78 (s, 3 H, CH_3); 4.65 (d, 1 H, H(2), J = 4.4 Hz); 5.40 (s, 1 H, H(10b)); 5.49 (m, 2 H, H(3), H(6)); 6.89 (d, 1 H, H(5), J = 7.7 Hz); 6.96 (m, 2 H, Ar); 7.13 (d, 1 H, H(7), J = 7.7 Hz); 7.22 (m, 1 H, H(9)); 7.29—7.37 (m, 3 H, H(8), H(10), Ar). ^{13}C NMR (DMSO-d_6), δ: 27.4, 35.9, 37.0, 46.3, 46.8, 49.2, 55.8, 56.2, 67.2, 69.7, 100.2, 112.4, 113.5, 114.1, 116.4, 123.6, 125.1, 126.3, 126.6, 126.8, 130.1, 132.5, 135.2, 151.9, 153.4, 210.6. Found (%): C, 76.22; H, 6.27; N, 7.97. $C_{33}H_{33}N_3O_3$. Calculated (%): C, 76.28; H, 6.40; N, 8.09.

3-(Adamantane-1-carbonyl)-2-(3,4,5-trimethoxyphenyl)-2,3-dihydropyrrolo[2,1-*a*]isoquinoline-1,1(10b*H*)-dicarbonitrile (7e). The isolated yield of the target product was 0.63 g (38%), m.p. 164—166 °C. ^{1}H NMR (DMSO-d_6), δ: 1.63 (m, 6 H, Ad); 1.75 (m, 6 H, Ad); 1.94 (m, 3 H, Ad); 3.69 (s, 3 H, CH_3); 3.83 (s, 6 H, 2 CH_3); 4.29 (d, 1 H, H(2), J = 5.9 Hz); 5.41 (d, 1 H, H(3), J = 5.9 Hz); 5.48 (d, 1 H, H(6), J = 7.7 Hz); 5.50 (s, 1 H, H(10b)); 6.76 (d, 1 H, H(5), J = 7.7 Hz); 6.94 (s, 2 H, Ar); 7.13 (d, 1 H, H(7), J = 7.3 Hz); 7.22 (m, 1 H, H(9)); 7.35 (m, 2 H, H(8), H(10)). ^{13}C NMR (DMSO-d_6), δ: 27.1, 35.6, 36.3, 45.9, 49.8, 54.1, 56.2, 60.0, 67.5, 69.7, 99.5, 106.8, 113.7, 123.3, 124.8, 126.1, 126.4, 129.0, 129.9, 132.4, 134.8, 137.9, 153.0, 211.4. Found (%): C, 74.20; H, 6.36; N, 7.60. $C_{34}H_{35}N_3O_4$. Calculated (%): C, 74.29; H, 6.42; N, 7.64.

1-(Adamantane-1-carbonyl)-2-phenyl-1,2-dihydropyrrolo-[1,2-*a*]quinoline-3,3(3a*H*)-dicarbonitrile (8b). The yield of the target product was 0.43 g (31%), m.p. 169—171 °C. ^{1}H NMR (DMSO-d_6), δ: 1.44—1.68 (m, 12 H, Ad); 1.82 (m, 3 H, Ad); 4.37 (d, 1 H, H(2), J = 6.9 Hz); 5.35 (d, 1 H, H(1), J = 7.0 Hz); 5.59 (m, 1 H, H(3a)); 5.90 (dd, 1 H, H(4), J = 10.1 Hz, J = 2.1 Hz); 6.11 (d, H(9), J = 8.0 Hz); 6.68 (m, 1 H, H(7)); 6.78 (d, 1 H, H(5), J = 10.1 Hz); 7.05 (d, 1 H, H(6), J = 7.3 Hz); 7.09 (m, 1 H, H(8)); 7.51 (m, 3 H, Ar); 7.72 (d, 2 H, Ar, J = 7.3 Hz). ^{13}C NMR (DMSO-d_6), δ: 27.1, 35.6, 37.4, 45.4, 48.9, 53.6, 62.0, 69.0, 109.8, 112.7, 116.3, 118.3, 119.3, 127.8, 128.9, 129.0, 129.4, 129.9, 130.1, 133.6, 140.5, 211.6. Found (%): C, 80.78; H, 6.13; N, 9.01. $C_{31}H_{29}N_3O$. Calculated (%): C, 81.02; H, 6.36; N, 9.14.

Two-component synthesis of benzannulated tetrahydroindolizines without isolation of intermediate products (method *D*). A flask equipped with a magnetic stirrer and reflux condenser was charged with ethanol (6 mL), then aromatic aldehyde (3.0 mmol), malononitrile (3 mmol), and triethylamine (3.3 mmol) were successively added with stirring. The reaction mixture was kept for 30 min at room temperature. A solution of isoquinoline or quinoline (3.0 mmol) and chloroacetone (3.0 mmol) in ethanol (1 mL) was prepared in a separate flask. The reaction mixture was carefully refluxed with stirring for 15 min, cooled, and added to the first reaction mixture. After stirring for 3.5 h at room temperature, the reaction mixture was worked-up as described in method ***A***.

3-Acetyl-2-phenyl-2,3-dihydropyrrolo[2,1-*a*]isoquinoline-1,1(10b*H*)-dicarbonitrile (10a). The product yield was 0.56 g

(55%), m.p. 153—154 °C. ^{1}H NMR (DMSO-d_6), δ: 2.17 (s, 3 H, CH_3); 4.44 (d, 1 H, H(2), J = 7.7 Hz); 5.06 (d, 1 H, H(3), J = 7.7 Hz); 5.40 (d, 1 H, H(6), J = 7.7 Hz); 5.72 (s, 1 H, H(10b)); 6.64 (d, 1 H, H(5), J = 7.7 Hz); 7.10 (d, 1 H, H(7), J = 7.5 Hz); 7.21 (m, 1 H, H(9)); 7.33 (m, 2 H, H(8), H(10)); 7.49 (m, 3 H, Ar); 7.60 (d, 2 H, Ar, J = 7.5 Hz). ^{13}C NMR (DMSO-d_6), δ: 26.9, 50.0, 51.8, 68.4, 73.3, 98.7, 113.4, 123.3, 124.8, 125.9, 126.2, 128.6, 129.0, 129.1, 129.8, 132.5, 133.7, 135.4, 205.4. Found (%): C, 77.82; H, 5.04; N, 12.35. $C_{22}H_{17}N_3O$. Calculated (%): C, 77.86; H, 5.05; N, 12.38.

3-Acetyl-2-(*p*-tolyl)-2,3-dihydropyrrolo[2,1-*a*]isoquinoline-1,1(10b*H*)-dicarbonitrile (10b). The product yield was 0.74 g (70%), m.p. 150—151 °C. ^{1}H NMR (DMSO-d_6), δ: 2.16 (s, 3 H, CH_3CO); 2.35 (s, 3 H, CH_3); 4.40 (d, 1 H, H(2), J = 8.1 Hz); 5.02 (d, 1 H, H(3), J = 8.1 Hz); 5.40 (d, 1 H, H(6), J = 7.7 Hz); 5.71 (s, 1 H, H(10b)), 6.63 (d, 1 H, H(5), J = 7.7 Hz); 7.11 (d, 1 H, H(7), J = 7.3 Hz); 7.20 (m, 1 H, H(9)); 7.28—7.33 (m, 4 H, H(8), H(10), Ar); 7.47 (d, 2 H, Ar, J = 7.7 Hz). ^{13}C NMR (DMSO-d_6), δ: 21.0, 27.3, 50.4, 52.0, 68.7, 73.5, 98.9, 113.8, 123.7, 125.2, 126.3, 126.5, 128.8, 130.0, 130.2, 131.0, 132.9, 135.8, 135.9, 205.8. Found (%): C, 78.21; H, 5.44; N, 11.85. $C_{23}H_{19}N_3O$. Calculated (%): C, 78.16; H, 5.42; N, 11.89.

Methyl 4-(3-acetyl-1,1-dicyanoo-1,2,3,10b-tetrahydropyrrolo[2,1-*a*]isoquinoline-2-yl)benzoate (10c). The isolated product yield was 0.84 g (71%), m.p. 145—146 °C. ^{1}H NMR (DMSO-d_6), δ: 2.21 (s, 3 H, CH_3CO); 3.87 (s, 3 H, CH_3); 4.57 (d, 1 H, H(2), J = 7.5 Hz); 5.14 (d, 1 H, H(3), J = 7.7 Hz); 5.44 (d, 1 H, H(6), J = 7.7 Hz); 5.76 (s, 1 H, H(10b)), 6.68 (d, 1 H, H(5), J = 7.7 Hz); 7.13 (d, 1 H, H(7), J = 7.7 Hz); 7.22 (m, 1 H, H(9)); 7.33 (m, 2 H, H(8), H(10)); 7.74 (d, 2 H, Ar, J = 8.4 Hz); 8.08 (d, 2 H, Ar, J = 8.4 Hz). ^{13}C NMR (DMSO-d_6), δ: 26.9, 49.9, 51.5, 52.3, 68.5, 73.4, 98.9, 113.2, 123.2, 124.9, 126.0, 126.3, 129.1, 129.8, 130.0, 132.5, 133.7, 135.4, 139.2, 165.7, 205.6. Found (%): C, 72.48; H, 4.79; N, 10.51. $C_{24}H_{19}N_3O_3$. Calculated (%): C, 72.53; H, 4.82; N, 10.57.

3-Acetyl-2-(3-bromo-4-methoxyphenyl)-2,3-dihydropyrrolo-[2,1-*a*]isoquinoline-1,1(10b*H*)-dicarbonitrile (10d). The isolated product yield was 0.83 g (62%), m.p. 146—147 °C. ^{1}H NMR (DMSO-d_6), δ: 2.17 (s, 3 H, CH_3CO); 3.39 (s, 3 H, CH_3); 4.42 (d, 1 H, H(2), J = 8.1 Hz); 5.05 (d, 1 H, H(3), J = 8.1 Hz); 5.39 (d, 1 H, H(6), J = 7.7 Hz); 5.68 (s, 1 H, H(10b)); 6.61 (d, 1 H, H(5), J = 7.7 Hz); 7.10 (d, 1 H, H(7), J = 7.3 Hz); 7.18—7.34 (m, 4 H, H(8), H(9), H(10), Ar); 7.59 (d, 1 H, Ar, J = 8.4); 7.79 (s, 1 H, Ar). ^{13}C NMR (DMSO-d_6), δ: 29.9, 50.0, 50.7, 56.4, 68.2, 73.0, 98.5, 111.0, 113.0, 113.3, 123.2, 124.8, 126.0, 126.2, 127.0, 129.6, 129.9, 132.5, 132.7, 135.4, 156.0, 205.4. Found (%): C, 61.68; H, 4.15; N, 9.41. $C_{23}H_{18}BrN_3O_2$. Calculated (%): C, 61.62; H, 4.05; N, 9.37.

3-Acetyl-2-(2,5-dimethoxyphenyl)-2,3-dihydropyrrolo[2,1-*a*]-isoquinoline-1,1(10b*H*)-dicarbonitrile (10e). The product yield was 0.85 g (71%), m.p. 148—150 °C. ^{1}H NMR (DMSO-d_6), δ: 2.22 (s, 3 H, CH_3CO); 3.74 (s, 3 H, CH_3); 3.79 (s, 3 H, CH_3); 4.71 (d, 1 H, H(2), J = 6.2 Hz); 5.15 (d, 1 H, H(3), J = 6.2 Hz); 5.45 (d, 1 H, H(6), J = 7.3 Hz); 5.58 (s, 1 H, H(10b)); 6.73 (d, 1 H, H(5), J = 7.3 Hz); 6.96 (m, 1 H, Ar); 7.05—7.15 (m, 3 H, H(7), Ar); 7.20 (m, 1 H, H(9)); 7.31 (m, 2 H, H(8), H(10). ^{13}C NMR (DMSO-d_6), δ: 26.8, 45.5, 49.1, 55.5, 55.9, 68.6, 73.7, 99.1, 112.4, 113.5, 113.9, 115.5, 123.5, 123.6, 124.8, 125.9, 126.5, 129.8, 132.5, 135.5, 151.7, 153.1, 205.8. Found (%): C, 72.22; H, 5.39; N, 10.49. $C_{24}H_{21}N_3O_2$. Calculated (%): C, 72.16; H, 5.30; N, 10.52.

3-Acetyl-2-(3,4,5-trimethoxyphenyl)-2,3-dihydropyrrolo-[2,1-*a*]isoquinoline-1,1(10b*H*)-dicarbonitrile (10f). The product yield was 0.43 g (34%), m.p. 136—138 °C. ^{1}H NMR (DMSO-d_6), δ: 2.19 (s, 3H, CH_3CO); 3.70 (s, 3 H, CH_3); 3.82 (s, 6 H, $2CH_3$); 4.39 (d, 1 H, H(2), J = 8.1 Hz); 5.09 (d, 1 H, H(3), J = 8.1 Hz); 5.42 (d, 1 H, H(6), J = 7.7 Hz); 5.68 (s, 1 H, H(10b)); 6.63 (d, 1 H, H(5), J = 7.7 Hz); 6.87 (s, 2 H, Ar); 7.12 (d, 1 H, H(7), J = 7.7 Hz); 7.22 (m, 1 H, H(9)); 7.32 (m, 2 H, H(8), H(10)). ^{13}C NMR (DMSO-d_6), δ: 26.9, 50.0, 52.2, 56.1, 60.1, 68.4, 73.1, 98.6, 106.2, 113.5, 123.3, 124.8, 126.0, 126.1, 129.1, 129.9, 132.6, 135.3, 153.1, 138.2, 205.3. Found (%): C, 70.00; H, 5.52; N, 9.86. $C_{25}H_{23}N_3O_4$. Calculated (%): C, 69.92.16; H, 5.40; N, 9.78.

3-Acetyl-2-(pyren-1-yl)-2,3-dihydropyrrolo[2.1-*a*]isoquinoline-1,1(10b*H*)-dicarbonitrile (10g). The isolated product yield was 0.85 g (61%), m.p. 159—161 °C. ^{1}H NMR (DMSO-d_6), δ: 2.21 (s, 3 H, CH_3); 5.37 (d, 1 H, H(2), J = 7.3 Hz); 5.54 (d, 1 H, H(3), J = 7.3 Hz); 5.86 (d, 1 H, H(6), J = 7.7 Hz); 5.98 (s, 1 H, H(10b)); 6.85 (d, 1 H, H(5), J = 7.7 Hz); 7.16—7.26 (m, 2 H, H(7), H(9)); 7.36 (m, 2 H, H(8), H(10)); 8.15 (m, 1 H, Ar), 8.25 (m, 2 H, Ar), 8.35—8.45 (m, 5 H, Ar), 8.81 (d, 1 H, Ar, J = 9.5 Hz). ^{13}C NMR (DMSO-d_6), δ: 31.5, 45.9, 50.0, 68.1, 69.0, 98.93, 113.0, 113.2, 121.9, 123.7, 124.2, 124.6, 124.8, 125.1, 125.4, 125.9, 126.0, 126.3, 127.4, 127.5, 127.8, 128.1, 129.0, 129.6, 130.4 130.6, 131.6, 131.8, 134.3, 134.6, 135.11, 199.4. Found (%): C, 83.06; H, 4.66; N, 9.12. $C_{32}H_{21}N_3O$. Calculated (%): C, 82.92; H, 4.57; N, 9.07.

3-Acetyl-2-(1*H*-indol-3-yl)-2,3-dihydropyrrolo[2.1-*a*]isoquinoline-1,1(10b*H*)-dicarbonitrile (10h). The product yield was 0.59 g (52%), m.p. 135—136 °C. ^{1}H NMR (DMSO-d_6), δ: 2.17 (s, 3 H, CH_3); 4.83 (d, 1 H, H(2), J = 8.1 Hz); 5.06 (d, 1 H, H(3), J = 8.1 Hz); 5.41 (d, 1 H, H(6), J = 7.7 Hz); 5.74 (s, 1 H, H(10b)); 6.63 (d, 1 H, H(5), J = 7.7 Hz); 7.09—7.31 (m, 6 H, H(7)—H(10), Ar); 7.44 (d, 1 H, Ar, J = 7.7 Hz); 7.77 (m, 2 H, Ar); 11.40 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6), δ: 26.9, 44.7, 49.6, 68.2, 73.7, 98.4, 111.1, 112.0, 113.1, 118.6, 119.1, 121.9, 122.6, 123.6, 125.0, 126.1, 126.7, 128.3, 129.8, 132.6, 133.5, 135.6, 205.2. Found (%): C, 76.28; H, 4.84; N, 14.90. $C_{24}H_{18}N_4O$. Calculated (%): C, 76.17; H, 4.79; N, 14.81.

1-Acetyl-2-phenyl-1,2-dihydropyrrolo[1,2-*a*]quinoline-3,3-(3a*H*)-dicarbonitrile (11a). The product yield was 0.32 g (31%), m.p. 165—167 °C. ^{1}H NMR (DMSO-d_6), δ:: 2.11 (s, 3 H, CH_3); 4.52 (d, 1 H, H(2), J = 8.8 Hz); 4.92 (d, 1 H, H(1), J = 8.8 Hz); 5.61 (m, 1 H, H(3a)); 5.87 (dd, 1 H, H(4), J = 10.3 Hz, J = 2.8 Hz); 6.34 (d, 1 H, H(9), J = 8.1 Hz); 6.70 (m, 1 H, H(7)); 6.81 (d, 1 H, H(5), J = 10.3 Hz); 7.07 (m, 2 H, H(8),H(6)); 7.50 (m, 3 H, Ar); 7.62 (d, 2 H, Ar, J = 5.5 Hz). ^{13}C NMR (DMSO-d_6), δ: 26.4, 48.9, 52.0, 68.2, 69.2, 110.1, 112.5, 115.5, 118.5, 118.6, 127.8, 128.7, 129.1, 129.4, 130.2, 130.3, 132.6, 141.4, 205.1. Found (%):C, 77.78; H, 4.99; N, 12.32. $C_{22}H_{17}N_3O$. Calculated (%): C, 77.86; H, 5.05; N, 12.38.

The use of method ***B*** and bromoacetone as the alkylating agent gave (see Table 3, entry *9*) 0.44 g (43%) of tetrahydroindolizine **11a**, m.p. 165—167 °C.

1-Acetyl-2-(*p*-tolyl)-1,2-dihydropyrrolo[2,1-*a*]quinoline-3,3(3a*H*)-dicarbonitrile (11b). The product yield was 0.65 g (62%), m.p. 162—164 °C. ^{1}H NMR (DMSO-d_6), δ: 2.09 (s, 3 H, CH_3CO); 2.36 (s, 3 H, CH_3); 4.47 (d, 1 H, H(2), J = 8.8 Hz); 4.89 (d, 1 H, H(1), J = 8.8 Hz); 5.59 (m, 1 H, H(3a)); 5.88 (dd, 1 H, H(4), J = 10.3 Hz, J = 2.6 Hz); 6.32 (d, 1 H, H(9),

J = 8.1 Hz); 6.69 (m, 1 H, H(7)); 6.80 (d, 1 H, H(5), J = 10.3 Hz); 7.07 (m, 2 H, H(8),H(6)); 7.32 (d, 2 H, Ar, J = 7.7 Hz); 7.52 (d, 2 H, Ar, J = 7.7 Hz). ^{13}C NMR (DMSO-d_6), δ: 20.7, 26.5, 49.0, 51.9, 68.2, 69.3, 110.2, 112.5 (CN), 112.6 (CN), 115.6, 118.6, 118.8, 127.8, 128.6, 129.5, 129.7, 130.2, 130.3, 139.1, 141.4, 205.1. Found (%): C, 78.10; H, 5.37; N, 11.84. $C_{23}H_{19}N_3O$. Calculated (%): C, 78.16; H, 5.42; N, 11.89.

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Received May 30, 2017;
in revised form August 21, 2017;
accepted September 27, 2017