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Synthesis of novel fluorescent 12a-aryl substituted indoxylisoquinolines via aryne-induced domino process

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Abstract: A novel effective protocol towards indolo[2,1-*a*]isoquinolinones via aryne-induced migration of aryl-anion in aryloxy substituted 3,4-dihydroisoquinolines is reported. These novel 12*a*-aryl substituted indoxylisoquinolines exhibit fluorescent properties and are characterized by green-shifted spectra and moderate quantum yields.

Introduction

Reactive intermediates such as radicals, carbenes, nitrenes etc. became widely used in organic synthesis. In recent decades arynes, highly reactive intermediates, justly converted from an object of purely theoretical interest into a reagent for synthesizing variously constructed *N*- and *O*-containing heterocycles[1] after the development of the synthetic method of Kobayashi et al.[2] Although [2+4] cycloaddition[3] and 1,3-dipolar cycloaddition[4] of arynes are used most frequently for heterocycle synthesis the nucleophilic addition to arynes is one of the oldest and still widely used approaches towards alkaloids and biologically active compounds.[5] The indolo[2,1-*a*]isoquinolines are the principal structural moieties of *Cryptaustoline* and *Cryptowoline* alkaloids,[6] which along with their synthetic analogs exhibit strong anticancer activity and affinity for estrogen receptors.[7]The structure of indoxylisoquinoline is also found in *Nuevamine* alkaloid (figure 1).[8] However the methods for the construction of such heterocycle core are limited.[9]

The low-lying LUMO determines highly electrophilic nature of arynes and makes them react primarily with electron-rich atoms of soft and neutral nucleophiles with the formation of zwitterions.[10] If the substrate has an electrophilic site, especially carbonyl or imine groups, then the anionic center of the zwitterion can attack it furnishing a fused heterocyclic system.[3f,4g, 5f,10h,i,11]

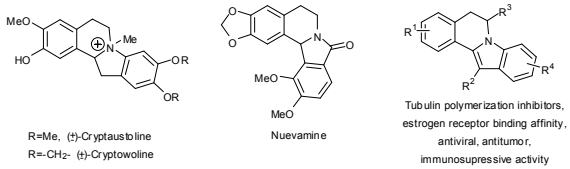

Figure 1 Biologically active indolo[2,1-*a*]isoquinolines

We presumed that the interaction of dehydrobenzene and derivatives thereof with the conjugated –N=C–C=O system in aryloxy substituted isoquinolines would lead to annulation of an indole moiety and construction of the attractive indoloisoquinoline core.

Herein we describe an elegant and effective synthesis of indoxylisoquinolines through Michael addition/aryl-anion migration domino protocol induced by arynes in 1-aryloxy substituted 3,4-dihydroisoquinolines.

Results and discussion

The required for the current study 1-(3,4-diethoxybenzoyl)-6,7-diethoxy-3,4-dihydriosoquinoline **1** was obtained via oxidation of drotaverine by atmospheric oxygen during its isolation from the commercially available hydrochloride; compound **2** was also received by oxidation protocol;[12] 1-benzoyl-3,3-dimethyl-substituted analogs **3**-**5** were synthesized by the literature methods[13] (figure 2). Compounds **5a** and **5b** were obtained from 3-methoxyphenyl 2-methylpropan-2-ol and represent an inseparable mixture of regioisomers. Arynes **6a-h** were studied in present work.

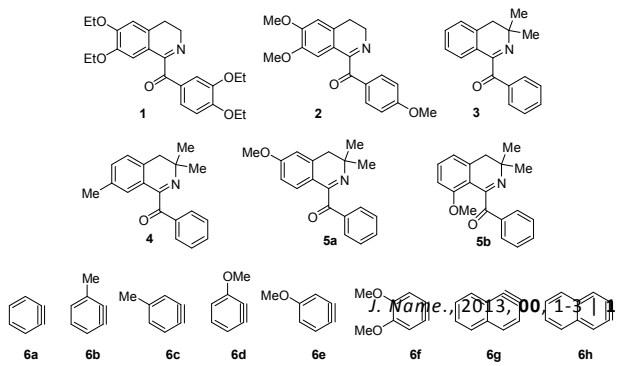

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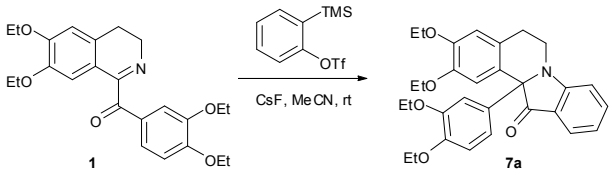
Figure 2. Starting 1-aryloxy-3,4-dihydroisoquinolines and arynes.

Based on the literature data the most used condition for generation of arynes is CsF in acetonitrile at room temperature. We conducted the model experiment with drotaveraldine **1** and benzyne **6a** at aforesaid conditions. To our delight the reaction proceeded smoothly to furnish an unusual indoxylisoquinoline **7a** in 90% yield (scheme 1).

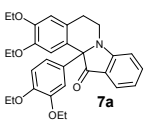
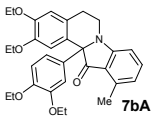
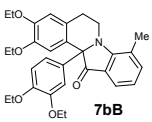
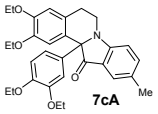
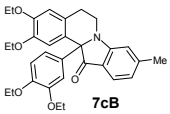
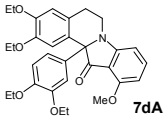
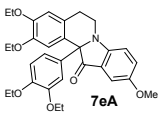
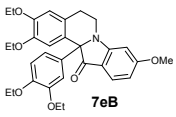
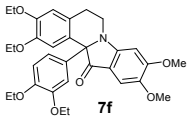
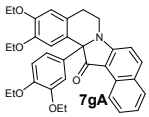
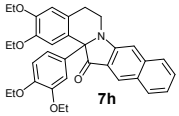
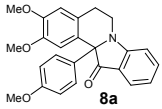
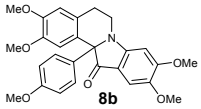
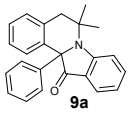
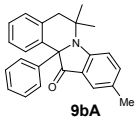
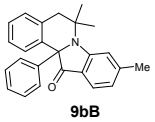
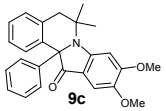
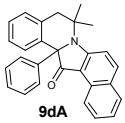
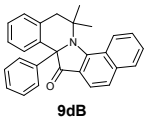
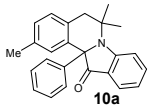
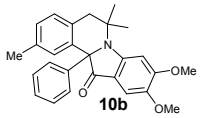
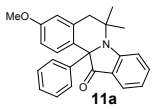
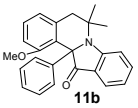


Scheme 1. The model synthesis of indoxylisoquinoline

In order to minimize the reaction time we tried some other conditions for aryne generation (see supporting information for details), but however the yields were comparable or lower, except benzyne **6h** (entry 8), which gave indoxylisoquinoline **7h** with good yields only in case of microwave irradiation.

Further studies of scope and limitations of the reaction were done in MeCN in the presence of CsF at room temperature, unless otherwise defined (Table 1).

Table 1. The structure and the yield of indolo[2,1-*a*]isoquinolinones

Entry	DIQ [a]	Aryne	Product	Yield, %
1	1	6a	 **7a**	90
2	1	6b	 **7bA**  **7bB**	70
3	1	6c	 **7cA**  **7cB**	75
4	1	6d	 **7dA**	67[b]
5	1	6e	 **7eA**  **7eB**	80
6	1	6f	 **7f**	85
7	1	6g	 **7gA**	87[b]
8	1	6h	 **7h**	67[c]
9	2	6a	 **8a**	73
10	2	6f	 **8b**	77
11	3	6a	 **9a**	93
12	3	6c	 **9bA**  **9bB**	91
13	3	6f	 **9c**	94
14	3	6g	 **9dA**  **9dB**	72
15	4	6a	 **10a**	69
16	4	6f	 **10b**	87
17	5a 5b	6a	 **11a**  **11b**	a:57 b:21

[a]DIQ-dihydroisoquinoline. [b] only one isomer of possible two isomers was isolated [c] CsF,

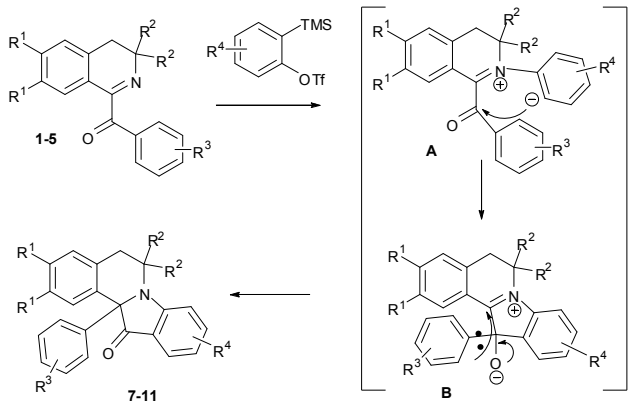
THF, 125°C, μW were used

The reaction proceeds smoothly and well tolerates the substituents in aryne moety. In case of compound **3** the target indoxylisoquinolines were formed faster compared to ethoxy- and methoxy substituted analogs and were precipitated from reaction mixtures.

It is noteworthy, that the unsymmetrical arynes **6d** and **6g** regioselectivly gave only one isomer. The regioselectivity could be explained in terms of the electronic and steric factors that favour the nucleophilic attack on the less hindered position.[3j,10h, 14]

Based on the literature data[3f,4g,5f,10a,b,h,j11] we suppose that the reaction starts with the nucleophilic attack of the isoquinoline nitrogen on generated in situ aryne leading to zwitterion **A**, the anionic center of which attacks further carbonyl group, giving oxy-anion **B**. Re-formation of the carbonyl group with subsequent migration of aryl substituent to C-12a-position leads to formation of indoloisoquinolinones **7-11** (scheme 2).

Migration of aryl anions during rearrangements of oxy-anions has been reported. Benzylic rearrangements of α-diarylketones through the action of bases[15] and quasi-Favorskii rearrangements of α-haloarylketones[16] are some examples.



Scheme 2 Plausible mechanism for the formation of the indolo[2,1-*a*]isoquinolines.

The structure of the product **10a** was unambiguously established by X-ray diffraction study and is shown in Figure 3 along with the atomic numbering schemes.

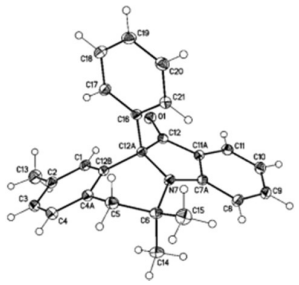


Figure 3.The X-ray structure of **10a**.

All synthesized in present work compounds displayed fluorescent properties both in solid state and in solution. Recently the fluorescent properties of indoloisoquinoline system were discribed.[17] In order to investigate the optical properties of obtained compounds the absorbance and emission spectra were recorded. It was found that the solutions of our indoxylisoquinolines are characterized by green-shifted spectra, except compound **7h**, that demonstrated more red shift. The quantum yield with the use of *p*-HOBDI-BF_2[18] as a standard was calculated (Table 2).

Table 2 Spectral properties of indolo[2,1-*a*]isoquinolinones in MeCN

Compound	Abs	Em	QY
7a	399 (4200)[a]	474	0.24
7dA	389 (3600)	466	0.22
7f	398 (6300)	479	0.26
7h	463 (1700)	581	0.26
8a	399 (3900)	478	**0.38**
8b	397 (5500)	481	**0.42**
9a	414 (4100)	465	0.23
9c	413 (5500)	476	**0.36**
9dA	423 (4400)	467	0.26
10a	413 (3800)	464	**0.42**
10b	413 (4800)	477	0.26
11a	413 (3600)	465	0.25

[a]Peak maximum in nm (extinction coefficient in $(mol\ cm)^{-1}$)

Conclusions

In summary, we developed a facile and efficient method for the synthesis of a new class of fluorescent 12a-aryl substituted indoxylisoquinolines through the interaction of arynes with 1-aroyl-3,4-dihydroisoquinolines resulted in annulation of an indolinone moiety that was accompanied by a shift of the aryl substituent from the isoquinoline 1-carbonyl. To the best of our knowledge this is the first example of the aryne-induced aryl anion migration. Further studies on the application of the present methodology along with the investigation of biological properties are in progress.

Acknowledgments

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