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Direct arylation of electron-poor indolizines

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ABSTRACT

Derivatized indolizines efficiently prepared via direct arylation, exhibit violet, blue or green fluorescence depending on the nature of substituents. By attaching two electron-withdrawing groups to five-membered ring it is possible to access a range of multi-substituted stable indolizine-based fluorophores. Compounds featuring this scaffold display advantageous combination of optical properties including reasonable fluorescence quantum yield combined with large Stokes shifts.

1. Introduction

The development of new molecular fluorescent sensor platforms for in vivo analysis of cells and in vitro analytical studies has emerged as an actively investigated research field in recent years.[1] As the applications for fluorescent probes in molecular biology (e.g., bioorthogonal labelling, selective detection of enzymes, cations, and antibodies) continue to increase, so does the need for dyes with diverse spectral and physicochemical properties. In particular, stable and biocompatible substances possessing high fluorescent quantum yield, large Stokes shift, and significant molar absorption coefficient are highly sought. Despite the multitude of available fluorophores, new fluorophoric systems are eagerly sought for more challenging applications, including single molecule imaging.[2] A key advantage of synthetic luminophores over natural fluorophores (such as tryptophan, fluorescent proteins, etc.) is the ability to use chemistry to dictate the properties and position of a fluorescent dye in a biological experiment. In addition to classic fluorescent platforms such as coumarins,[3] fluoresceins,[4] and bodipys,[5] researchers have also explored new scaffolds.[6] One particularly interesting one is indolizine, which, thanks to its high fluorescent quantum yield, has attracted attention from many vantage points.[7] In particular, indolizino[3,4,5-*ab*]isoindoles prepared from pyrido[2,1-*b*]isoindoles have been found to be excellent fluorophores with a high quantum yield.[8] Recently, other similar indolizine-based fluorescent dyes have been described.[9] The chemistry of this class of molecules, although well-known,[10] continues to attract attention.[11]

New reactions undoubtedly offer unique tools in both the synthesis of aromatic compounds as well as in their functionalization, directed both towards medicinal as well as materials chemistry. One of the newest methodologies relies on direct arylation of aromatic heterocycles.[12] Various aromatic systems, such as pyrrole, indole, thiophene, imidazole, etc., have been successfully arylated to smoothly give biaryl linkages.[13,14]

For functional dyes based on an indolizine core to fulfil their full potential, the issues of both stability and the ability to fine-tune the fluorescence have to be addressed. The promising optical properties of both unsubstituted indolizine as well as some of its derivatives prompted us to investigate whether electron-poor indolizines could also be effectively arylated to afford a library of functional dyes combining beneficial optical properties with increased stability. Herein we would like to present the results of this investigation.

2. Results and discussion

Indolizines are significantly less studied than indoles, which are also mirrored in the progress made in their direct arylation. In 2003, Gevorgyan and co-workers were the first to report a synthetic protocol devoted to this subject, demonstrating that both

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indolizine and its simple derivatives can be efficiently arylated in the presence of $Pd(PPh_3)_2Cl_2$ as the catalyst.[15] Additional examples of the same process, albeit under different conditions, were published later.[16] More recently, direct arylation of the indolizine core was also achieved via arylotrifluoroboranes.[17] Taking into consideration the plausible mechanism of this reaction,[13] it is not at all clear if compounds bearing multiple electron-withdrawing groups (hence with lowered average electron density) will undergo this reaction. Finally, we also queried whether arylation with dibromoarenes can be performed, affording dyes constructed of two indolizine units spanned with π-linkers.

The synthetic objective corroborated the optical goal, which was based on the necessity to increase oxidation potential via the introduction of multiple electron-withdrawing groups. This particular choice was mostly based on the desire to investigate the regioselectivity of direct arylation. Given these objectives, we chose the following indolizine derivatives as pivotal building blocks: 2-cyanoindolizine (**1a**),[18] diethyl indolizine-1,2-dicarboxylate (**1b**),[19] 1-cyano-2-ethoxycarbonylindolizine (**1c**),[20] 2-(4-trifluoromethyl ophenyl)indolizine (**1d**) and 1,2,3-tris(methoxycarbonyl)indolizine (**1e**)[21] (Fig. 1).

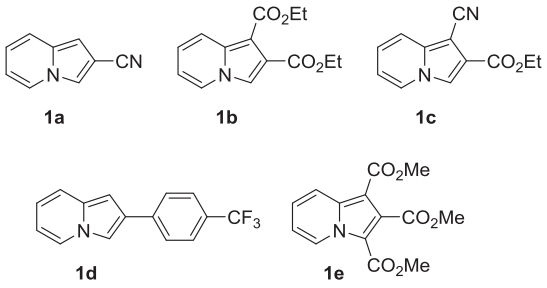


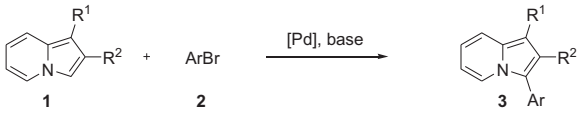
Fig. 1. Structures of indolizine building blocks.

Analysis of the literature inclined us to perform the direct arylation of compounds **1a**–**d** using three distinct methodologies: (a) Gevorgyan's method for the arylation of indolizine;[15] (b) Doucet's, low palladium loading method[22] for the arylation of electron-rich heterocycles (including pyrrole,[23] indole, furan and thiophene groups);[24] and (c) a process mediated by *tert*-butanolates, reported earlier by our group, which showed peculiar regioselectivity with regard to unsubstituted indolizine.[16b]

From the synthetic point of view, we were eager to investigate direct arylation using both electron-poor aromatic haloarenes (which are more reactive in these reactions) as well as electron-rich ones. This aspect was also critical given the photophysical aim of this study. Consequently, the following bromoarenes were chosen: 1-bromo-4-nitrobenzene, 4-bromobenzonitryle, 3-bromobenzonitryle, 5-acetyl-2-bromothiophene, 4-bromoanisol and 4-bromo-*N*,*N*-diphenylaniline. 1-Bromonaphthalene was also selected as a representative of sterically hindered arylating agents. We also wished to entertain the possibility of performing a model reaction between indolizine derivatives and exemplary dibromoarenes, namely 2,7-dibromo-9,9-dioctylfluorene (**5a**) and 2,5-dibromothiophene (**5b**).

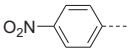
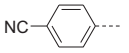
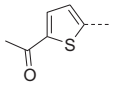
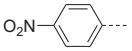
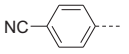
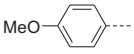
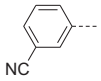
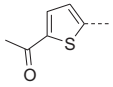
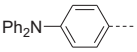
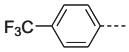
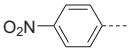
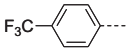
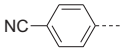
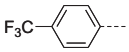
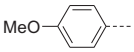
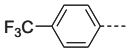
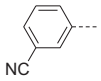
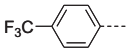
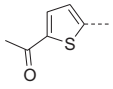
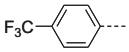
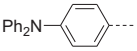
In all cases, palladium-catalyzed reactions led to the expected arylated products (Table 1, methods A and B). It turned out that the low catalyst-loading protocol, originally reported for pyrroles,[23] showed better efficiency with electron-poor halides (Table 1, method B). On the other hand, for aryl bromides bearing electron-donating groups, better yields were achieved using Gevorgyan's method[15] (Table 1, method A). Most importantly, the presence of two electron-withdrawing groups at positions 1 and 2 still allowed us to obtain the corresponding 3-arylated products in good yields (Table 1, entries 8–17).

Table 1
Results of the direct arylation of indolizines **1a**–**d**



Entry	Indolizine	R^1	R^2	Bromoarene	Ar	Product	Meth. A	Meth. B
1	**1a**	H	CN	**2a**	O_2N–	**3aa**	99%	96%
2	**1a**	H	CN	**2b**	NC–	**3ab**	85%	88%
3	**1a**	H	CN	**2c**	MeO–	**3ac**	80%	76%
4	**1a**	H	CN	**2d**	NC–	**3ad**	82%	83%
5	**1a**	H	CN	**2e**	O, S	**3ae**	70%	82%
6	**1a**	H	CN	**2f**	Ph_2N–	**3af**	64%	73%
7	**1a**	**H**	CN	**2g**		**3ag**	80%	69%

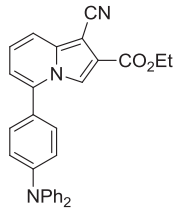
Table 1 (*continued*)

Entry	Indolizine	R^1	R^2	Bromoarene	Ar	Product	Meth. A	Meth. B
8	**1b**	CO_2Et	CO_2Et	**2a**		**3ba**	94%	88%
9	**1b**	CO_2Et	CO_2Et	**2b**		**3bb**	67%	67%
10	**1b**	CO_2Et	CO_2Et	**2e**		**3be**	48%	50%
11	**1b**	CO_2Et	CO_2Et	**2g**		**3bg**	24%	64%
12	**1c**	CN	CO_2Et	**2a**		**3ca**	81%	73%
13	**1c**	CN	CO_2Et	**2b**		**3cb**	68%	71%
14	**1c**	CN	CO_2Et	**2c**		**3cc**	26%	31%
15	**1c**	CN	CO_2Et	**2d**		**3cd**	60%	70%
16	**1c**	CN	CO_2Et	**2e**		**3ce**	40%	55%
17	**1c**	CN	CO_2Et	**2f**		**3cf**	58%	38%
12	**1d**	H		**2a**		**3da**	71%	96%
13	**1d**	H		**2b**		**3db**	56%	91%
14	**1d**	H		**2c**		**3dc**	50%	43%
15	**1d**	H		**2d**		**3dd**	83%	94%
16	**1d**	H		**2e**		**3de**	95%	92%
17	**1d**	H		**2f**		**3df**	53%	75%

Method A. **1**/**2**=1:1.2, $PdCl_2(PPh_3)_2$, KOAc, NMP, H_2O, 100 °C, 16 h.[15]
Method B. **1**/**2**=1.5:1, $Pd(OAc)_2$, KOAc, DMAc, 130 °C, 20 h.[23]

Following the protocol developed for the arylation of *N*-alkylpyrroles and consisting of using *t*-BuOLi/DMF at a higher temperature,[16b] we could not obtain any identifiable products in the attempted arylation of indolizines **1a**–**d**. The reactions suffered from low conversion and/or a complex mixture of products, which probably originated from the hydrolysis of CO_2Et and CN groups.

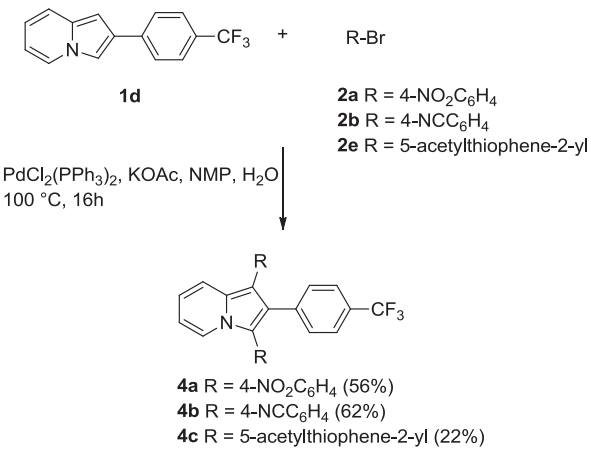
Surprisingly, when indolizine **1c** was reacted with 4-bromo-*N*,*N*-diphenylaniline (**2f**), in addition to the expected 3-arylated indolizine **3cf**, the corresponding 5-arylation product **3cf'** was obtained, albeit in low yield (Fig. 2). This unexpected result cannot be easily rationalized.



3cf'

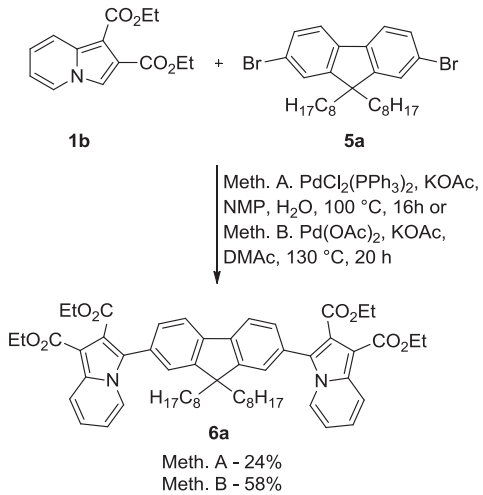
Fig. 2. Structure of product **3cf**.

We wondered whether an indolizine already possessing an electron-withdrawing aromatic substituent could be subjected to the stepwise bis-arylation, potentially leading to the corresponding 1,2,3-tris-arylindolizines. The inherent difference in the substrate ratio of the two main protocols (arene/bromoarene=1:1.2[15] and 1.5:1[23]), suggested that the Gevorgyan method would serve us better in this particular case. Indeed, the expected products were obtained following a slightly modified version of protocol A; it turned out that the incorporation of exclusively electron-poor aromatic groups (**4a**, **4b** and **4c**) was possible (Scheme 1). The attempts at the bis-arylation of indolizine **1d** with 3-bromobenzonitrile (**2d**) or 4-bromoanisole (**2c**) led to a mixture of undesired mono-arylated (major) and bisarylated (trace) products.

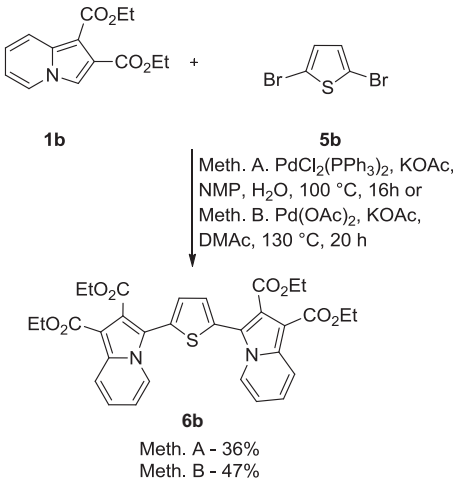


Scheme 1. Bis-arylation of indolizines.

Moreover, we demonstrated the possibility of efficient and convenient preparation of dyes constructed of two indolizine units connected with arene linkers. Direct coupling of indolizine **1b** with dibromoarenes **5a** and **5b** was attempted under both Doucet's[23] and Gevorgyan's[15] conditions, as shown in Schemes 2 and 3. As a result, we obtained structurally unique bis-indolizines **6a** and **6b** in satisfactory yields. It is noteworthy that, in both cases, substantially higher yields were obtained under low palladium loading conditions.[23]



Scheme 2. Preparation of bis-indolizine **6a**.



Scheme 3. Preparation of bis-indolizine **6b**.

Aiming to investigate arylation proceeding at the C5 carbon, we tested the reactivity of 1,2,3-tris(methoxycarbonyl)-indolizine (**1e**). It possesses ester groups at all the positions of the five-membered ring, which decrease electron density and hence reactivity. In spite of numerous attempts, experiments performed on indolizine **1e** using palladium-catalyzed protocols[15,23] did not afford any products. In the case of the *t*-BuOLi-mediated procedure,[16b] an extremely complex mixture was obtained, likely related to the liability of ester groups under strongly basic conditions.

The effect of structural variations on photophysical properties was studied in detail for all new indolizines (Table 2, Figs. 3 and 4). Acetonitrile was chosen as the solvent for the measurements due to its ability to dissolve all the tested compounds, making it possible to investigate the relationship between the structure and optical properties of these molecules.

Table 2
Optical properties of the arylated indolizines in CH_3CN

Product	$\lambda_{max\ abs}$/nm	ε/M^{-1} cm^{-1}	$\lambda_{max\ em}$/nm	Stokes shift/cm^{-1}	Φ_{fl}/%[a]
3aa	403	9600	—	—	—
3ab	359	12,400	455	5950	39
3ac	315	9300	439	8970	10
3ad	335	8500	437	7150	15
3ae	383	13,600	497	5720	9
3af	344	22,200	454	6960	9
3ag	336	6300	443	7460	17
3ba	347	10,400	—	—	—
3bb	340	15,600	443	6930	21
3be	351	11,800	490	7920	14
3bg	330	9200	418	6290	16
3ca	353	9300	—	—	—
3cb	339	9200	430	6070	29
3cc	356	4800	429	6540	15
3cd	336	6500	412	5500	21
3ce	350	10,200	482	7990	5
3cf	328	19,000	463	8710	10
3da	429	7100	—	—	—
3db	369	7700	479	6900	6
3dc	323	4300	448	8600	8
3dd	345	6200	484	8920	2
3de	390	6600	—	—	—
3df	336	3900	465	6270	6
4a	423	17,300	—	—	—
4b	364	14,000	483	6770	8
4c	399	14,600	—	—	—
6a	345	42,500	425	5500	47
6b	343	22,800	472	7880	6

[a] Determined using quinine sulfate as the standard.

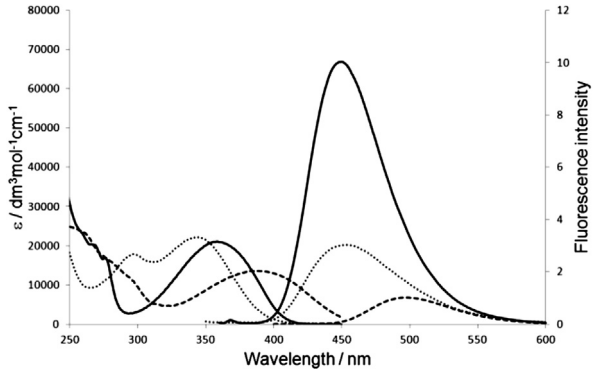


Fig. 3. Absorption and emission of compounds **3ab** (solid line), **3af** (dotted line) and **3ae** (dashed line) in MeCN (excitation wavelength 315 nm for **3ab** and 343 nm for **3af** and **3ae**).

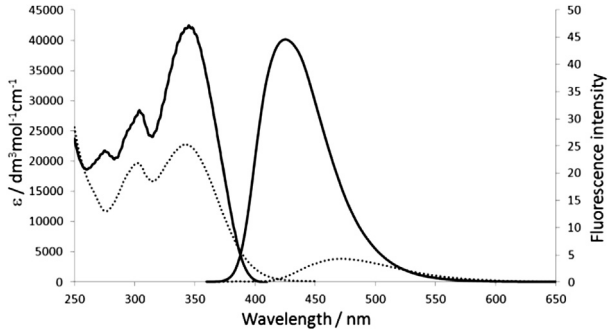


Fig. 4. Absorption and emission of compounds **6a** (solid line), **6b** (dotted line) in MeCN (excitation wavelength 345 nm).

All investigated compounds possessed a strong absorption band, which was typically located between 300 and 400 nm. Moreover, significant expansion of the π-system (for **6a** and **6b**) was mirrored in the higher extinction coefficients. A strong impact of the electron-withdrawing groups (reflected in the bathochromic shift of the absorption band) could be easily detected in the absorption spectra of **3ba**, **3bb**, **3be**, **3cb**, **3cd** and **3ce**. These results indicate that the five-membered ring of indolizine, even possessing two electron-withdrawing substituents, still retains its intrinsic electron-excessive nature. The presence of electron-withdrawing substituents at position 3 formed weak push–pull systems, which are known to have bathochromically shifted absorption.[1c] The clear tendency was that the 4-nitrophenyl substituent shifted the absorption bathochromically the most, such that λ_{max} reached 430 nm. In principle, λ_{max} decreases following the order NO_2>Ac>CN>OMe>NPh_2 (Table 2, Fig. 3).

All the investigated molecules, except for compounds bearing a 4-nitrophenyl substituent (**3ba**, **3da**, **3aa** and **3ca**), emitted violet, blue or blue-green light. The absence of fluorescence for the 4-nitrophenyl compounds was not surprising due to the known quenching effect of the nitro group.[1c] For the majority of the new indolizines, the emission maxima were situated in the violet-blue region. However, for the dyes **3ae**, **3be** and **3ce** possessing a 5-acetylthiophene group, λ_{em} was shifted bathochromically to the green region. The effect of this group on the bathochromic shift of absorption and emission was stronger than for the 4-cyanophenyl substituent (**3be** and **3ce** vs **3bb** and **3cb**). This probably originates from the geometry of the thiophene ring, which allows for a smaller mean angle between the five-membered ring of indolizine and the thiophene ring (compared to the benzene ring). At the same time, it allows for a higher degree of planarization in the excited state, which translates to a stronger emission shift hence a larger Stokes shift for these molecules. Although the keto group is known to quench fluorescence since the n→π* transition has the lowest energy (Strickler–Berg equation),[1c] most of the compounds possessing the 5-acetylthiophene moiety (**3be**, **3ae** and **3ce**) displayed noticeable fluorescence quantum yields (Table 2, Fig. 3). This was not true, however, for dyes **3de** and **4c**, which did not display any fluorescence. These variations are strongly related to the fact that n→π* and π→π* transitions are probably energetically close and slight changes of the structure can invert their order. The diesters possessed low to moderate fluorescence quantum yields.

As was expected, in contrast to other scaffolds, the α-naphthyl substituent (present in compounds **3bg** and **3ag**), with a steric nature that prevents the overlap of orbitals, did not alter the absorption maxima. Moreover, even in the excited state, the interaction between naphthalene and indolizine was prevented, which was mirrored in the position of the emission maxima (λ_{em} was strongly shifted hypsochromically in contrast to other arylated analogues).

The comparison of the properties of 2-cyanoindolizines with structurally related 1-cyano-2-carboxyethyl- and 1,2-bis(carboxyethyl)indolizines revealed that the fluorescence quantum yields for the these molecules were generally lower, with the notable exception of 2-cyano-3-(4-cyanophenyl)-indolizine (**3ab**, Φ_{fl}=39%). In this group of compounds, the correlations between the values of the molar extinction coefficients and the Stokes shift were particularly clear, showing that a higher value of ε leads to a smaller Stokes shift. This can probably be explained by a lower affinity for a change in conformation in the exited state. For arylated 2-(4-trifluoromethylphenyl)indolizines, Φ_{fl} turned out to be consistently low.

Regarding the optical properties of tri-arylated indolizines **4a**–**c**, bearing one 4-trifluoromethylophenyl substituent, the influence of substituents on λ_{abs} followed the general trends (i.e., the presence of electron-withdrawing groups caused a bathochromic shift of the absorption band, which for **4a** and **4b** moved them into the visible region). Triaryl-substituted indolizines **4a**–**c** did not possess more red-shifted absorption when compared with monoaryl substituted indolizines, which most probably occurred due to the lower degree of planarization.

The comparison of diesters **3ba**–**3bg** with the structurally similar mono-esters **3ca**–**3cf** showed that for the latter compounds, the emission was slightly hypsochromically shifted. Whenever possible, the comparison of dyes possessing 3-cyanophenyl versus 4-cyanophenyl moieties shows that the latter ones possess more bathochromically shifted absorption and higher fluorescence quantum yields (Table 2).

One of the bis-indolizines, compound **6a**, displayed the highest fluorescence quantum yield (Table 2, Fig. 4). It is noteworthy to add that the λ_{abs} of arylated indolizines is shifted bathochromically compared to their pyrrole analogues, such as 3-(4-trifluorophenyl)-*N*-methylpyrrole[25] or 2-(4-methoxyphenyl)pyrrole.[26]

3. Conclusion

We demonstrated that the presence of two electron-withdrawing groups at positions 1 and 2 does not deactivate indolizines towards direct arylation. Under the reaction conditions optimized for electron-rich heterocycles, we obtained the expected arylated products in good yields with very good regioselectivity. Still, when all positions in the five-membered ring were occupied by ester groups, the reaction did not proceed at the six-membered ring under any of the tested conditions. For the first time, we have reported bis-arylation of the 2-arylindolizine core leading to the corresponding 1,2,3-trisaryloindolizines in good yields. The low palladium loading method developed by Doucet and co-workers was preferred for the synthesis of bis-indolizines from

dibromoarenes. Due to the significant expansion of the π-system, these molecules were characterized by increased ε.

We have demonstrated that by arranging various substituents, it is possible to easily manipulate the emission characteristics of indolizine derivatives with λ_{max} ranging from 420 nm to 500 nm. The derivatization of indolizine with substituted aryl rings at positions 3 and 1 leads to compounds possessing very low fluorescence quantum yields. Consequently, dyes bearing ester/cyano groups were shown to have more attractive optical properties.

The replacement of one ester group at position 1 of the indolizine core with CN did not affect absorption, but hypsochromically shifted emission (~10–20 nm). At the same time, Φ_{fl} remained at a similar level. Systematic optical studies of multiply substituted indolizines showed that most of these compounds were characterized with large Stokes shifts. One of the most promising compounds, possessing a fluorene bridge, had high fluorescence quantum yield (47%) while its Stokes shift remained relatively large (5500 cm^{-1}). The addition of an additional aryl ring at position 1 to 2,3-diarylindolizines did not shift absorption but considerably increased ε. The other notable findings are that, in most cases, the five-membered ring of the indolizine chromophore behaves as an electron-rich moiety, forming push–pull systems with electron-poor aryl substituents (which results in bathochromically shifted absorption and emission, when compared with other compounds). In addition to tuning the intrinsic emission properties of indolizine, it is also possible to influence the Stokes shift by incorporating various groups into the core.

4. Experimental section

4.1. General procedures for the synthesis of 3-arylindolizines

Method A:[15] A solution of indolizine (0.85 mmol, 1 equiv), aryl bromide (1.02 mmol, 1.2 equiv) and KOAc (166 mg, 1.7 mmol, 2 equiv) was placed in a Schlenk tube previously flushed with argon. Subsequently, NMP (1.7 ml) and $PdCl_2(PPh_3)_2$ (30 mg, 5 mol %, 42.5 μmol) were added and resulting solution was stirred at 100 °C for 10 min under an argon atmosphere. Afterwards, water (27 μl, 1.7 mmol, 2 equiv) was added to the reaction mixture and heating was continued overnight at 100 °C. After reaction completion, the residue was diluted with dichloromethane, washed with water, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by means of flash column chromatography.

Method B:[23] A solution of the corresponding aryl bromide (0.85 mmol, 1 equiv), indolizine (1.28 mmol, 1.5 equiv), KOAc (166 mg, 1.7 mmol, 2 equiv) and $Pd(OAc)_2$ (2.9 mg, 12.8 μmol, 1.5 mol %) was placed in a Schlenk tube previously flushed with argon. Subsequently, DMAc (2.55 ml) was added and the resulting mixture was stirred at 130 °C for 20 h under an argon atmosphere. After reaction completion, the residue was diluted with dichloromethane, washed with water, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by means of flash column chromatography.

Method C:[16b] Aryl bromide (0.6 mmol, 1 equiv) and indolizine (9 mmol, 15 equiv) were placed in a glass tube previously flushed with argon. Subsequently 750 μl of a stock solution of the base in DMF (containing 1.2 mmol of *t*-BuOLi) was added. The resulting reaction mixture was stirred overnight at 145 °C. Subsequently, it was evaporated under reduced pressure and purified by column chromatography.

Bis-arylation of indolizines was performed according a slightly modified procedure:[15] A solution of indolizine (0.425 mmol, 1 equiv), aryl bromide (0.85 mmol, 2 equiv) and KOAc (83 mg, 0.85 mol, 2 equiv) was placed in a Schlenk tube previously flushed with argon. Subsequently, NMP (0.85 ml) and $PdCl_2(PPh_3)_2$ (15 mg, 5 mol %, 21.2 μmol) were added and the resulting solution was stirred at 100 °C for 10 min under an argon atmosphere. Afterwards, water (15 μl, 0.85 mmol, 2 equiv) was added to the reaction mixture and heating was continued overnight at 100 °C. After reaction completion, the residue was diluted with dichloromethane, washed with water, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by means of flash column chromatography.

*4.1.1. 1,3-Bis(4-nitrophenyl)-2-(4-trifluoromethylphenyl)-indolizine (**4a**).* Following the general procedure, indolizine **1b** (222 mg, 0.85 mmol) and 1-bromo-4-nitrobenzene **2a** (343 mg, 1.70 mmol) were reacted. The crude product was purified by means of flash column chromatography (SiO_2, CH_2Cl_2/hexanes, 1:1). All fractions containing the expected product were collected and rechromatographed (SiO_2, AcOEt/hexanes, 1:4, 1:2) affording 242 mg (56%, recrystallized from AcOEt/hexanes) of **4a**. R_f=0.46 (SiO_2, CH_2Cl_2/hexanes, 1:1), mp 242 °C (AcOEt/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.71 (7, *J*=6.7 Hz, 1H, ind), 6.98 (dd, J_1=8.6 Hz, J_2=6.9 Hz, 1H, ind), 7.13 (d, *J*=7.9 Hz, 2H, C_6H_4), 7.34 (d, *J*=8.8 Hz, 2H, C_6H_4), 7.47 (m, 2×2H, C_6H_4), 7.66 (d, *J*=9.1 Hz, 1H, ind), 8.15 (d, *J*=7.4 Hz, 1H, ind), 8.17 (d, *J*=8.8 Hz, 2H, C_6H_4), 8.26 (d, *J*=8.8 Hz, 2H, C_6H_4). ^{13}C NMR (125 MHz, $CDCl_3$): δ 112.6, 113.1, 117.8, 121.3, 121.5, 122.4, 123.9, 124.4, 125.5, 127.0, 129.3, 129.5, 130.3, 131.1, 131.2, 132.1, 136.9, 137.3, 141.3, 145.8, 147.0. HRMS (EI) obsd 503.1093 [$M^{\bullet+}$], calcd 503.1093 ($C_{27}H_{16}F_3N_3O_4$). UV–vis (CH_3CN): λ_{max} ($\varepsilon\times10^{-3}$) 423 (17.3) nm.

*4.1.2. 1,3-Bis(4-cyanophenyl)-2-(4-trifluoromethylphenyl)-indolizine (**4b**).* Following the general procedure, indolizine **1d** (111 mg, 0.425 mmol) and 4-bromobenzonitrile **2b** (155 mg, 0.85 mmol) were reacted. The crude product was purified by means of flash column chromatography (SiO_2, CH_2Cl_2/hexanes, 1:4, 1:3), affording 123 mg (62%, recrystallized from AcOEt/hexanes) of **4b**. R_f=0.6 (SiO_2, CH_2Cl_2/hexanes, 3:1), mp 227–228 °C (AcOEt/hexanes); ^{1}H NMR (500 MHz, DMSO): δ 6.80 (t, *J*=6.8 Hz, 1H, ind), 7.04 (t, *J*=7.8 Hz, 1H, ind), 7.23, 7.54 (AA′BB′, *J*=7.8 Hz, 2×2H, C_6H_4), 7.35, 7.62 (AA′BB′, *J*=7.9 Hz, 2×2H, C_6H_4), 7.66 (d, *J*=9.0 Hz, 1H, ind), 7.78, 7.90 (AA′BB′, *J*=7.9 Hz, 2×2H, C_6H_4), 8.21 (d, *J*=7.1 Hz, 1H, ind). ^{13}C NMR (125 MHz, DMSO): δ 108.2, 110.4, 111.9, 113.0, 117.2, 118.6, 119.0, 121.4, 121.7, 122.9, 123.1, 125.2, 125.8, 127.2, 127.5, 130.3, 130.9, 131.4, 131.5, 132.3, 132.9, 134.5, 138.0, 138.9. HRMS (EI) obsd 463.1306 [$M^{\bullet+}$], calcd 463.1296 ($C_{29}H_{16}F_3N_3$). UV–vis (CH_3CN): λ_{max} ($\varepsilon\times10^{-3}$) 367 (14.0) nm.

*4.1.3. 1,3-Bis(5-acetyltiophen-2-yl)-2-(4-trifluoromethylphenyl)-indolizine (**4c**).* Following the general procedure, indolizine **1b** (222 mg, 0.85 mmol) and 5-acetyl-2-bromothiophene **2e** (349 mg, 1.70 mmol) were reacted. The crude product was purified by means of flash column chromatography (SiO_2, CH_2Cl_2/hexanes, 1:1). All fractions containing the expected product were collected and rechromatographed (SiO_2, AcOEt/hexanes, 2:3) affording 93 mg (22%, recrystallized from AcOEt/hexanes) of **4c**. R_f=0.5 (SiO_2, CH_2Cl_2), mp 177–178 °C (AcOEt/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.52 (s, 3H, Ac), 2.55 (s, 3H, Ac), 6.91 (d, *J*=3.4 Hz, 1H, thiophene), 6.74 (t, *J*=6.5 Hz, 1H, ind), 6.95 (d, *J*=3.2 Hz, 1H, thiophene), 7.02 (t, *J*=7.6 Hz, 1H, ind), 7.33, 7.55 (AA′BB′, *J*=8.2 Hz, 2×2H, C_6H_4), 7.54 (m, 1H, thiophene), 7.62 (d, *J*=3.2 Hz, 1H, thiophene), 7.90 (d, *J*=9.0 Hz, 1H, ind), 8.29 (d, *J*=7.1 Hz, 1H, ind). ^{13}C NMR (125 MHz, $CDCl_3$): δ 26.5, 26.7, 107.1, 113.1, 116.1, 118.3, 121.6, 123.3, 125.3, 126.7, 128.5, 129.6, 129.8, 129.9, 131.2, 132.5, 132.6, 133.1, 137.5, 138.9, 142.2, 144.9, 145.0, 190.3, 190.4. HRMS (EI) obsd 509.0727 [$M^{\bullet+}$], calcd 509.0731 ($C_{27}H_{18}F_3NO_2S_2$). UV–vis (CH_3CN): λ_{max} ($\varepsilon\times10^{-3}$) 399 (14.6) nm.

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Supplementary data

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