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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).

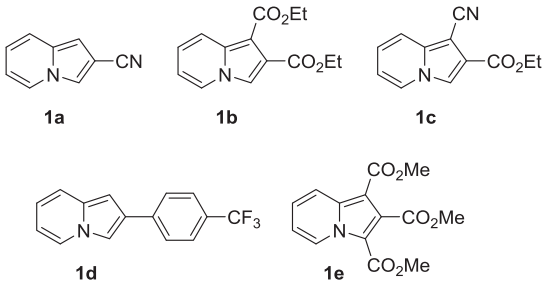


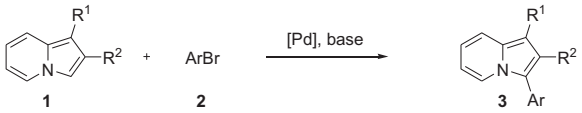
Fig. 1. Structures of indolizine building blocks.

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%