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Novel NHC-mediated synthesis of pyrrolo[2,1-a]isoquinolines and their photophysical investigations.

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Dedicated to Professor R. H. Sahasrabudhey in commemoration of his birth centenary

Abstract: An NHC-mediated synthesis of pyrrolo[2,1-a]isoquinoline and indolizine derivatives with potential biological activity is reported. The preliminary photophysical studies of these compounds reveal that they have potential application in the sensing of Volatile Organic Compounds (VOCs).

Pyrrolo[2,1-a]isoquinoline derivatives constitute an important class of heterocyclic compounds, primarily due to the remarkable biological properties of the lamellarine group of alkaloids that are endowed with this framework.[1] Inter alia, they have been reported to inhibit topoisomerase,[2] HIV and integrase.[3] Some other members of the group have been shown to possess antiimflammatory,[4] cardiovascular[5] and antidepressant[6] properties. Some selected biologically relevant pyrroloisoquinoline related compounds are shown in Figure 1. In addition to biological activities, these π-conjugated molecules possess excellent photophysical properties which can play potential role in various applications such as optoelectronics, sensing, etc.[7] Not surprisingly, there has been enormous interest in the synthesis of pyrrolo[2,1-a]isoquinoline derivatives.[8] Although a number of protocols have been developed for their synthesis, most of the endeavours relied on Huisgen [3+2] dipolar cycloaddition reactions.[9] A special mention may be made of the visible light mediated strategies employed by Xia,[10a] Glorius,[10b] Itoh[10c] and Yang.[10d]

In the context of the recent discovery of NHC-mediated annulation of enals to a variety of electrophiles resulting in the synthesis of a wide range of carbo and heterocyclic compounds in several laboratories, including our own,[11] it was of interest to explore such a strategy for the construction of pyrrolo-[2,1-a]isoquinolines. The successful culmination of our efforts in this direction constitutes the subject matter of this communication.

In a prototype experiment, DBU (50 mol%) was added to a suspension of 4-methoxycinnamaldehyde **1a** (0.225 mmol), 2-(2-ethoxy-2-oxoethyl)isoquinolin-2-ium bromide **2a** (0.15 mmol), and IMes.HCl **3a** (15 mol%) in DCM and this mixture was stirred for 24h at room temperature. The reaction mixture upon column chromatography afforded the product, ethyl 2-(4-methoxyphenyl)pyrrolo[2,1-a]isoquinoline-3-carboxylate **4a**, as a white crystalline solid in 19% yield (Scheme 1).

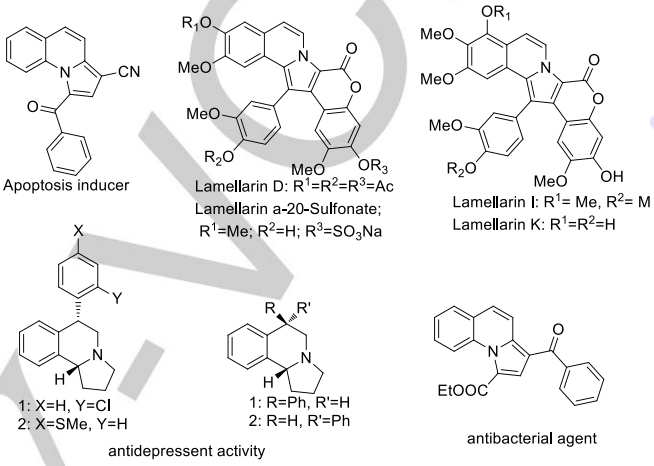
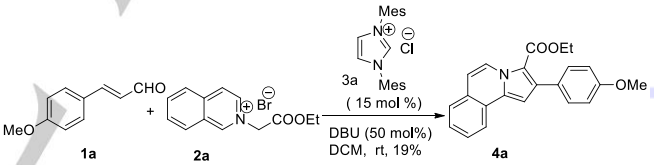


Figure 1. Biologically active pyrroloisoquinoline related compounds.



Scheme 1. NHC-mediated synthesis of pyrrolo[2,1-a]isoquinoline.

The structure **4a** was established by single crystal X-ray data (Figure 2) and all spectra features are consistent with it.

Figure 2. ORTEP diagram of **4a**.

In view of the pleasant result, detailed optimization studies were undertaken. For this, commonly available NHC precursors **3a−f** were used for screening (Table 1). Among the six catalysts investigated, benzimidazolium catalyst **3c** exhibited high catalytic activity (Table 1, entry 3). After identifying NHC precursor **3c** as the optimal catalyst, the influence of solvent was studied. Among the solvents tested, THF furnished the desired product in good yield (Table 1, entry 7, 77%). Other solvents such as CH_3CN, chloroform, toluene and DME afforded the product in moderate yields (Table 1, entries 8, 9, 10 and 11).

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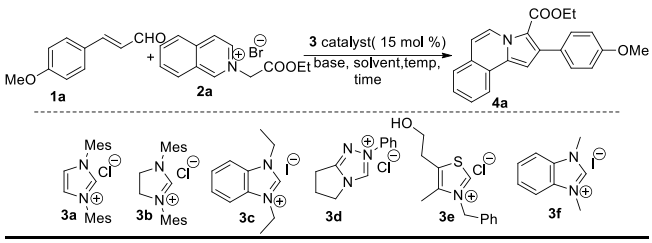
Subsequently, we examined the effect of bases on the reaction. Among the five bases tested, DBU furnished the desired product in good yield. Finally it was found that raising the temperature of the reaction resulted in a lower yield of product (table 1, entry 16). Based on the above results, it was clear that the formation of pyrroloisoquinoline carboxylate in higher yield was facilitated by the combination of benzimidazolium precatalyst **3c** and DBU in THF as the solvent at room temperature (entry 7).

Table 1. Condition Optimization[a]



Entry	Catalyst	base, solvent,temp., time (h)	Yield (%)[b]
1	**3a**	DBU, DCM, rt, 24	19
2	**3b**	DBU, DCM, rt, 24	26
3	**3c**	DBU, DCM, rt, 24	55
4	**3d**	DBU, DCM, rt, 24	11
5	**3a**	DBU, DCM, rt, 24	21
6	**3a**	DBU, DCM, rt, 24	30
7	**3a**	DBU, THF, rt, 12	77
8	**3a**	DBU, CH_3CN, rt, 24	52
9	**3a**	DBU, $CHCl_3$, rt, 24	38
10	**3a**	DBU, Toluene, rt, 24	45
11	**3a**	DBU, DME, rt, 24	31
12	**3a**	KO^tBu, THF, rt, 24	13
13	**3a**	K_2CO_3, THF, rt, 24	23
14	**3a**	DMAP, THF, rt, 24	24
15	**3a**	NEt_3, THF, rt, 12	71
16	**3b**	DBU, THF, 65 ^oC, 12	35

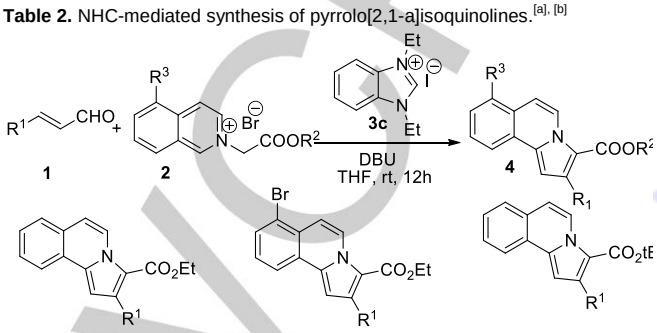
[a] Reaction conditions: **1a** (0.225 mmol), **2a** (0.15 mmol), carbene precursor (15mol %), base (50mol%) in 2 mL of solvent. [b] isolated yield.

Subsequent studies were focused on the scope of the reaction. As shown in Table 2, the reaction works well for a range of enals having electron-withdrawing or electron donating substituents on the 4th position of β-aryl ring. The reaction proceeds smoothly for 5-bromo-2-(2-ethoxy-2-oxoethyl)isoquinolin-2-ium bromide (**4i**-**4k**). In all the cases products were obtained in moderate to good yields.

The scope of the reaction was further explored by employing pyridine moiety instead of isoquinoline (Table 3). It was found that the method was successful in the synthesis of various substituted phenylindolizine carboxylates in good yields (**6a**-**6e**).

A plausible mechanism for the reaction may be advanced as follows (Scheme 2). Initially the homoenolate **I** generated by the reaction of enal with NHC undergoes aerial oxidation to form the acyl azolium intermediate **II**.[12] The latter on Michael type reaction with isoquinolinium ylide delivers the tetrahydropyrroloisoquinoline derivative **III.** Subsequent nucleophilic addition to the carbonyl group of **III** followed by the ejection of NHC leads to the carbonyl derivative of tetrahydropyrroloisoquinoline **IV**. Conceivably on two consecutive aerial oxidations[8j, 13] of the latter afforded the desired pyrolloisoquinoline derivative **VII**.

Table 2. NHC-mediated synthesis of pyrrolo[2,1-a]isoquinolines.[a], [b]



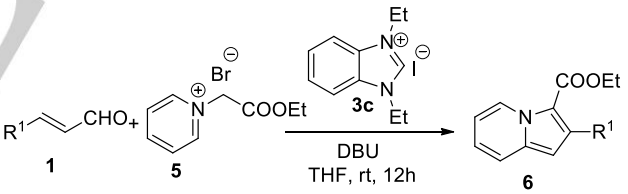
R1 = 4-MeO-Ph, **4a**, 77%
2-MeO-Ph, **4b,** 71%
thienyl, **4c,** 83%
4-F-Ph, **4d**, 90%
furyl, **4e,** 66%
4-Me-Ph, **4f,** 71%
Naphthyl, **4g,** 71%
Me, **4h**, 71%

R1 = 4-MeO-Ph, **4i,** 80%
furyl, **4j**, 68%
thienyl, **4k,** 69%

R1 = 4-MeO-Ph, **4l**, 82%
2-MeO-Ph, **4m,** 71
furyl, **4n,** 68%
4-F-Ph, **4o**, 87%
thienyl, **4p**, 82%
4-NO_2-Ph, **4q**, 55%
4-Cl-Ph, **4r,** 71%

[a] Reactions were carried out with **1** (0.225 mmol), **2** (0.15 mmol), **3c** (15 mol%), DBU (50 mol%) in 2 mL of THF (stirred for 12h at rt). [b] isolated yield.

Table 3. NHC mediated synthesis of indolizines. [a], [b]



R^1 = 4-MeO-Ph, **6a,** 75%
4-F-Ph, **6b**, 66%

R^1 = Furyl, **6c,** 65%
4-Cl-Ph, **6d,** 74%

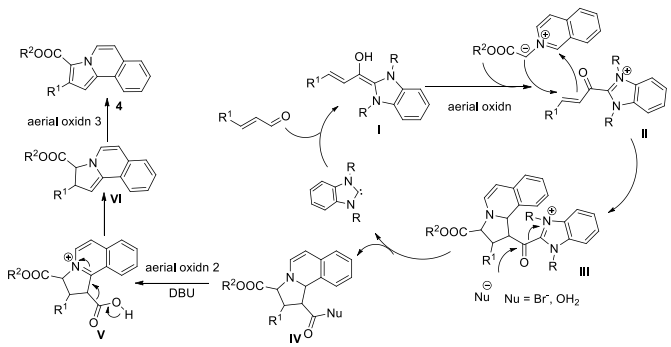
R^1 = 2-MeO-Ph, **6e,**

[a] Reactions were carried out with **1** (0.225 mmol), **5** (0.15 mmol), **3c** (15 mol%), DBU (50 mol%) in 2 mL of THF (stirred for 12h at rt). [b] isolated yield.

As already stated, pyrrolo[2,1-a]isoquinoline based compounds are well known for their biological properties such as cytotoxicity, cell differentiation inhibition, etc. However, only limited attempts have been made to understand the photophysical properties of these compounds. In view of this, we have carried out preliminary photophysical investigation, of the series of pyrrolo[2,1-a]isoquinoline derivatives accessed by synthesis.

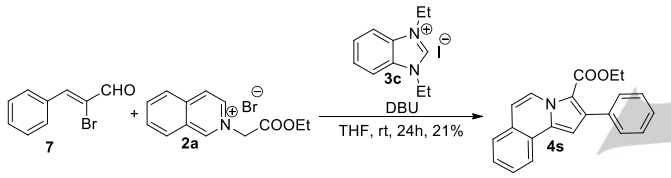
The absorption spectrum of **4l** showed three peaks at 279 (λ_{max}), 350 and 369 nm in $CHCl_3$ solution at concentration of 1×10^{-4} M. The emission spectrum of **4l** exhibited two emission peaks at 379 and 395 nm with a shoulder band around 416 nm. The life time measurement of **4l** solution in $CHCl_3$ provided a

value of 2.16 ns. The fluorescence quantum yield of **4l** measured as 68%.



Scheme 2. Mechanism of the reaction.

To shed some light on the mechanism of the reaction, we carried out an experiment with 2-bromoenal **7** and 2-(2-ethoxy-2-oxoethyl)isoquinolin-2-ium bromide **2a** in presence of benzimidazolium catalyst **3c** and DBU in THF (Scheme 3.). This reaction afforded the product as ethyl 2-phenylpyrrolo[2,1-a]isoquinoline-3-carboxylate in 21% yield. This experiment provides support for the intermediacy of α, β-unsaturated acyl azolium invoked in Scheme 2.[14]



[a] Reaction was carried out with **7** (0.225 mmol), **2a** (0.15 mmol), **3c** (15 mol%), DBU (50 mol%) in 2 mL of THF (stirred for 24h at rt). [b] isolated yield.

Scheme 3. Reaction of isoquinolium salt with 2-bromo enal. [a], [b]

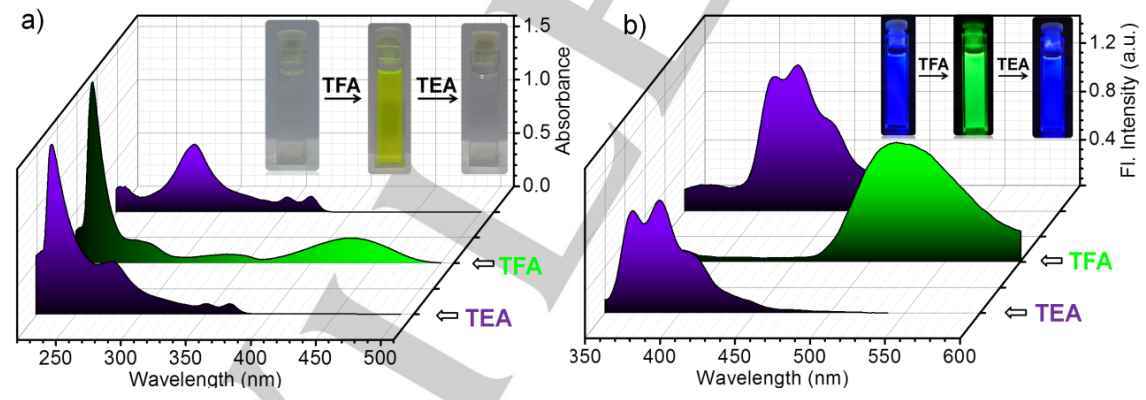


Figure 3. Absorption (a) and emission (b) spectra of **4l** with the addition of 1 eq. of trifluoroacetic acid (TFA) and 1 eq. of triethyl amine (TEA) in $CHCl_3$. Insets of Figure 3a and b show color changes after addition of TFA and TEA under ambient and UV light respectively.

The absorption spectrum of **4l** showed three peaks at 279 (λ_{max}), 350 and 369 nm in $CHCl_3$ solution at concentration of 1×10^{-4} M. The emission spectrum of **4l** exhibited two emission peaks at 379 and 395 nm with a shoulder band around 416 nm. The life time measurement of **4l** solution in $CHCl_3$ provided a value of 2.16 ns. The fluorescence quantum yield of **4l** measured as 68%.

Interestingly, it was observed that the colorless $CHCl_3$ solution of **4l** changed to bright green while adding 1 equivalent (eq.) of trifluoroacetic acid (TFA) (Figure 3a). This change was reversible with the addition of 1 eq. of triethylamine (TEA). After addition of TFA, all the three absorption peaks (279, 350 and 369 nm) of **4l** decreased and became broad in nature. At the same time, a new absorption band appeared around 430 nm. Similarly, the emission bands (379, 395, and 416 nm) were vanished and a new emission band was appeared around 520 nm (Figure 3b). We also observed the visual emission color change from a mixture of violet and blue to green. To study the periodic changes of the absorption and emission spectra in the presence of TFA and TEA, a titration experiment was carried out with various equivalents of TFA and TEA (Figure 4). Each addition of TFA (0.1 eq. of TFA) resulted in the periodic decrease in the absorption peaks at 279, 350 and 369 nm and periodic increase in the absorption peak at 430 nm. Even 0.3-0.5 equivalents of TFA were good enough to give considerable changes in the absorption and fluorescence spectra (Figure 4). The recovery of the absorption peak at 279, 350 and 369 nm was observed while adding $CHCl_3$ solution of TEA. The changes of emission spectra while adding TFA and TEA were indicated in the Figure 4b. It clearly show that the periodic decrease in the emission peaks at 379, 395, and 416 nm and increase of the same at 520 nm upon addition of TFA and vice versa upon addition of TEA.

All other derivatives showed similar changes in the absorption and emission spectra with the addition of TFA and TEA (see supporting information). These changes in the photophysical properties could be attributed to the nitrogen atom in the poly heterocyclic ring being protonated and deprotonated upon addition of TFA and TEA respectively. In order to study the ability of these compounds to act as acid sensors in film state, we drop casted the $CHCl_3$ solution of **4l** in a quartz substrate and the resultant film was exposed to saturated vapours of various volatile acids (trifluoroacetic acid, formic acid, acetic acid, propionic acid and butric acid. The changes in the emission intensities at 395 and 520 nm after exposure (30 sec) were measured and compared (Figure 5). Among these acids, TFA showed better sensing ability because of its higher vapour pressure and higher acidity compared to other acids. This film could be reused several times after exposing to air for 3 to 5 minutes. For practical application, the same film can be prepared on filter paper strip by drop casting the chloroform solution and used to detect volatile acids (Figure 5b). Thus, the preliminary photophysical studies reveal that these compounds have potential application in the sensing of VOCs (Volatile Organic Compounds) such as acetic acid, substituted propionic acid, etc, which are biomarkers present in the exhaled breath of cancer patients.[15, 16] A detailed investigation regarding sensing ability of these fluorescent compounds are in progress.

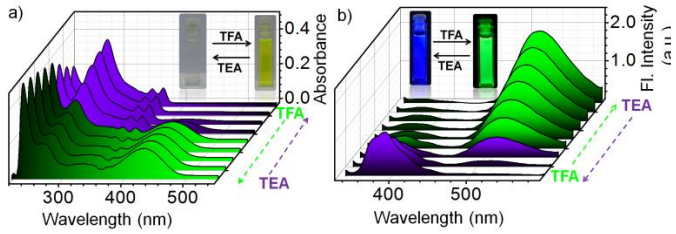


Figure 4. (a) Absorption and (b) emission spectra of **4l** with the addition of various (0.1 – 1) equivalents of trifluoroacetic acid and triethyl amine in $CHCl_3$. Insets of Figure 4a and b show color changes of **4l** upon addition of TFA and TEA, under ambient and UV light respectively.

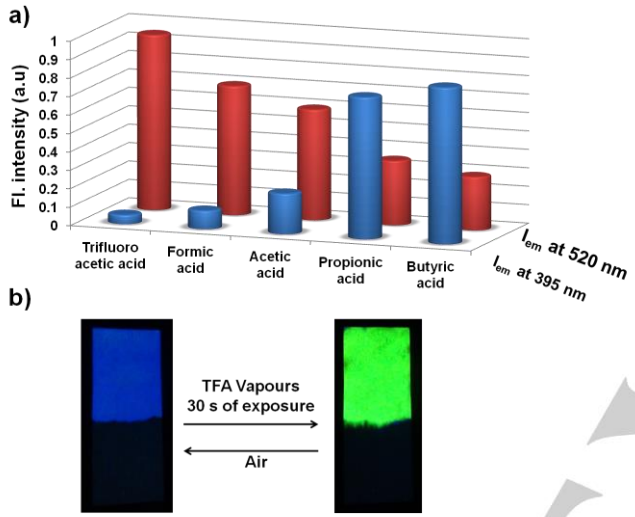


Figure 5. a) 3D plot of emission changes of **4l** film drop casted in quartz after exposing to various volatile acids; b) Photograph shows visual emission change of **4l** coated on filter paper strip after exposing to saturated vapours of TFA for 30 seconds.

In conclusion, we have developed a facile synthesis of pyrrolo[2,1-a]isoquinolines and indolizines with potential biological activities. The simple and mild reaction conditions and the good yields of products are likely to make the reaction attractive for its application in the synthesis of a variety of natural and unnatural pyrrolo[2,1-a]isoquinolines and indolizines. The preliminary photophysical studies reveal that these compounds have potential application in the sensing of VOCs which are biomarkers present in the exhaled breath of cancer patients.

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Keywords: N-heterocyclic carbenes • indolizines •pyrrolo[2,1-a]isoquinolines • Organocatalysis • acyl azolium

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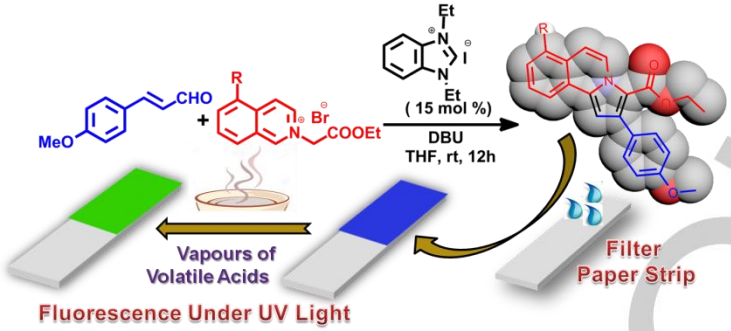

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Page No. – Page No.

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