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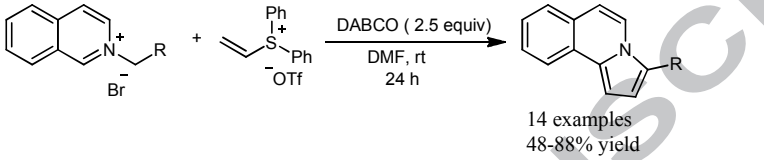

14 examples
48-88% yield

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Direct synthesis of pyrrolo[2,1-*a*]isoquinolines by 1,3-dipolar cycloaddition of stabilized isoquinolinium N-ylides with vinyl sulfonium salts

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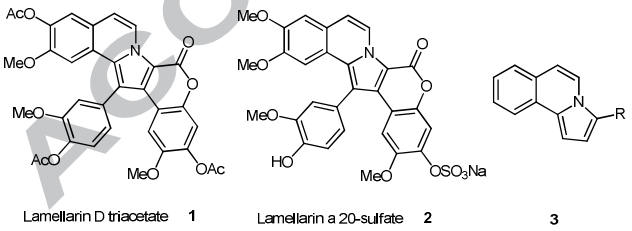
ABSTRACT

A direct and efficient synthesis of 2,3-unsubstituted 1-acylpyrrolo[2,1-*a*]isoquinolines is described. The 1,3-dipolar cycloaddition of stabilized isoquinolinium N-ylides with vinyl sulfonium salts features simple experimental procedures, mild conditions and moderate to good yields.

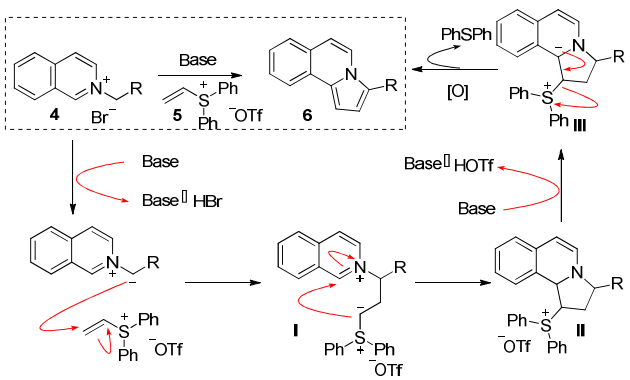
Pyrrolo[2,1-*a*]isoquinolines constitute the backbone of the Lamellarin class of marine alkaloids[1] which have exhibited anticancer and antiviral activity[2] and are considered as privileged heterocycles broadly used in pharmaceutical and material science[3] (Scheme 1). Therefore, these important frameworks have become targets of interest in the organic synthetic community. Over the past decades, various synthetic methods for the construction of pyrrolo[2,1-*a*]isoquinolines[4-7] have been developed, including the [3+2] cycloaddition of isoquinolinium N-ylides with electron-deficient alkynes or alkenes,[4] 1,5-electrocyclization[5] and several transition metal catalyzed C-N bond formation reactions.[6]



Scheme 1. Structures of lamellarins and scaffold **3**.

Among them, only a few examples are related to the direct construction of 2,3-unsubstituted pyrrolo[2,1-*a*]isoquinolines **3**, which are important precursors[3b] for the synthesis of potent cytotoxic analogues of the marine alkaloid Lamellarin D. Conventional methods for the synthesis of 2,3-unsubstituted pyrrolo[2,1-*a*]isoquinolines required multiple steps or using special alkene substrates such as nitroketene dithioacetals followed by desulfurization with raney-nickel.[4g,4h] Very recently, Xu developed a method to generate a variety of 2,3-unsubstituted 1-acylpyrrolo[2,1-*a*]isoquinolines by the reaction of isoquinolinium ylide with maleic anhydride in the presence of the oxidant tetrakispyridinecobalt(II) dichromate.[8] However, this elegant method required an excess of oxidant and high temperature. Thus, the further development of more efficient and mild approaches to synthesize 2,3-unsubstituted pyrrolo[2,1-*a*]isoquinolines remains a worthwhile goal.

In the past few years, vinyl sulfonium salts[9] have been established as valuable and versatile intermediates for organic synthesis. For instance, Aggarwal and co-workers[10] have developed a series of reaction pathways involving vinyl sulfonium salts resulting in the synthesis of morpholines, oxazepines and imidazolinium salts. On the other hand, this reagent can also be used for the synthesis of α-imidostyrenes by michael addition, 1,2-H shift and an elimination sequence.[9l,9m]

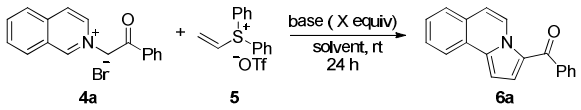


Scheme 2. Reaction design.

In pursuing our ongoing program on carbon- and heterocycle oriented methodology development,[11] we envisioned that the electrophilic vinylsulfonium salt **5** should react with isoquinolium ylides derived from the isoquinolium salts **4**, to form intermediate **II** under basic conditions. Then intermediate **III** would be expected to be formed with another equivalent of base. Subsequent elimination of Ph_2S and dehydroaromatization could afford 2,3-unsubstituted pyrrolo[2,1-*a*]isoquinolines **6**. We herein report the realization of this strategy for the direct synthesis of 2,3-unsubstituted 1-acylpyrrolo[2,1-*a*]isoquinolines.

We initially studied the reaction of 2-(2-oxo-2-phenylethyl)isoquinolin-2-ium bromide **4a** and the vinylsulfonium salt **5** in CH_3CN, in the presence of *t*-BuOK (2.5 equiv) at room temperature for 24 h. As highlighted in Table 1, the base had a dramatic impact on the reaction efficiency. After screening several organic and inorganic bases, DABCO (1, 4-diazabicyclo[2.2.2]octane) was identified as the ideal choice (Table 1, entries 1-6). A survey of solvents revealed that DMF was optimal (Table 1, entries 6-10). The reaction conditions were further optimized by adjusting the amount of the base. As expected, there was nearly no conversion when 1.0 equiv of DABCO was used (Table 1, entry 11). On the other hand, increasing the amount of the base did not lead to improvement of the reaction efficiency (Table 1, entry 13).

Table 1. Optimization of the reaction conditions[a]



4a **5** **6a**

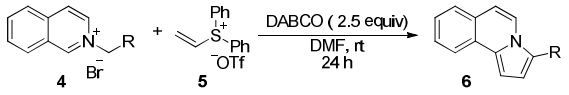
Entry	Base	X	Solvent	Yield[b] (%)
1	*t*-BuOK	2.5	CH_3CN	39
2	NaH	2.5	CH_3CN	36
3	Cs_2CO_3	2.5	CH_3CN	39
4	KOH	2.5	CH_3CN	45
5	Et_3N	2.5	CH_3CN	20
6	DABCO	2.5	CH_3CN	52
7	DABCO	2.5	CH_2Cl_2	33
8	DABCO	2.5	THF	59
9	DABCO	2.5	DMF	62
10	DABCO	2.5	CH_3OH	15
11	DABCO	1.0	DMF	trace
12	DABCO	2.0	DMF	50
13	DABCO	3.0	DMF	63

[a] Reaction conditions: **4a** (0.30 mmol), **5** (0.36 mmol), base (1.0-3.0 equiv), solvent (4.0 mL). DABCO = 1, 4-diazabicyclo[2.2.2]octane.

[b] Yield of isolated product.

With the optimal conditions established, the scope of the isoquinolium ylides derived from the isoquinolium salts was explored. As summarized in Table 2, this cyclization process appeared to be tolerant with respect to significant structural variations in the isoquinolium salts and furnished the corresponding 2,3-unsubstituted 1-acylpyrrolo[2,1-*a*]isoquinolines in moderate to good yield. The acyl group with electron-rich substitutents could be successfully utilized for this transformation (Table 2, entries 2 and 3). Moreover, incorporation of halogen groups at various positions of the acyl benzene ring indicated that steric modification of the acyl group could be accomplished without compromising reaction efficiency (Table 2, entries 4-10). Furthermore, it was found that the aryl framework could be extended to heterocycle-derived substrates, affording products **6k** and **6l** in 63% and 65% yield, respectively (Table 2, entries 11-12). It is well known that the trifluoromethyl

Table 2. Synthesis of 2,3-unsubstituted 1-acylpyrrolo[2,1-*a*]isoquinolines[a]



4 **5** **6**

Entry	Substrate	Product	Yield[b] (%)
1	**4a**	**6a**	62
2	**4b**	**6b**	63
3	**4c**	**6c**	61
4	**4d**	**6d**	65
5	**4e**	**6e**	63
6	**4f**	**6f**	58
7	**4g**	**6g**	88
8	**4h**	**6h**	64
9	**4i**	**6i**	73
10	**4j**	**6j**	66
11	**4k**	**6k**	63
12	**4l**	**6l**	65
13	**4m**	**6m**	63
14	**4n**	**6n**	48

[a] Reaction conditions: **4** (0.30 mmol), **5** (0.36 mmol), DABCO (0.75 mmol), CH_3CN (4.0 mL). DABCO = 1, 4-diazabicyclo[2.2.2]octane.

[b] Yield of isolated product.

group could affect the biological activity of compounds. The trifluoromethylacyl ylides could also be successfully employed in this process and afforded the product in 63% yield (Table 2, entry 13). The cyano-derived ylide was tolerated for this cycloaddition to produce the corresponding product which should be valuable for further chemical transformations.

In summary, we have developed a direct and efficient synthesis of 2,3-unsubstituted 1-acylpyrrolo[2,1-*a*]isoquinolines by 1,3-dipolar cycloaddition of stabilized isoquinolinium N-ylides with vinyl sulfonium salts. This process features simple experimental procedures, under mild conditions. Application of this reaction to the preparation of biologically relevant compounds is currently underway in our laboratory.

Acknowledgments

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