Organic LETTERS

Letter

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Modular Approach to 9-Monosubstituted Fluorene Derivatives Using Mo^{V} Reagents

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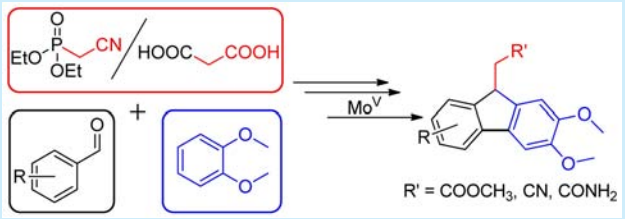
Supporting Information

ABSTRACT: Oxidative coupling using molybdenum(V) reagents provides fast access to highly functionalized 9-monosubstituted fluorenes. This synthetic approach is highly modular, is high yielding, and tolerates a variety of labile moieties, e.g. amides or iodo groups. The established protocol leads to promising precursors for pharmacologically important analogues of melatonin.



Applications of fluorenes and their synthesis have attracted a significant interest within the past decades. The fluorene core is well-known for its important role in protecting groups for peptide and oligosaccharide synthesis.[1] In addition, a variety of bioactive compounds involve the fluorene moiety.[2] Fluorene derivatives such as **1** act as calcium antagonists analogue to the drug verapamil.[3] Other studies show that *N*-(2-(fluoren-9-yl)ethyl)-propanamides **2** provide the same chronobiotical activity as melatonin.[4] Recently, the unique properties of fluorene as a building block have been used to design a wide range of optoelectronic devices such as organic field effect transistors (OFET) and organic light emitting diodes (OLED).[5,6] Furthermore, the introduction of a fluorene group significantly improves the two-photon absorption cross section of organic chromophores.[7]

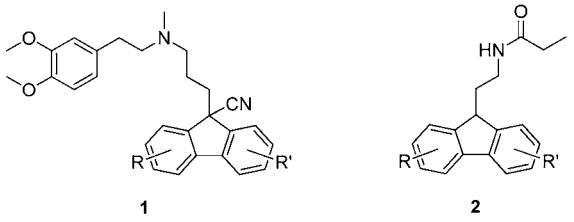
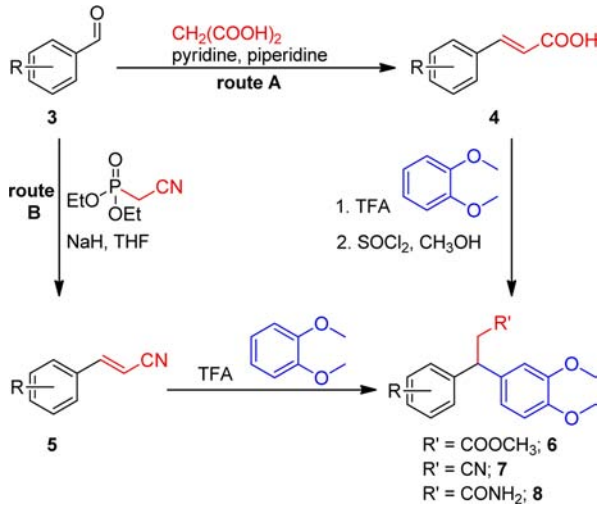


Figure 1. Examples for bioactive fluorene derivatives.

Scheme 1. Modular Synthesis of the Starting Materials



Although plenty of synthetic strategies for the construction of fluorenes are known, the synthesis turns out to be difficult for specific substitution patterns. Specifically, the synthesis of highly functionalized 9-monosubstituted fluorene derivatives often involves tedious multistep sequences and harsh reaction conditions.[8] The scope of accessible structures has significantly increased due to several transition metal catalyzed reactions, which were reported in the past decades.[9−11] Despite this improvement, the substrate scope of those reactions is often limited to the accessibility of the precursor equipped with leaving groups.[12] Recently, a Rh-catalyzed 2-fold C,H-activation is described to be suitable for 9-disubstituted fluorenes, but the synthesis of 9-monosubstituted derivatives using this particular method is unfavorable due to lower yields, longer reaction times, and a limited substitution pattern.[13] Therefore, a new and versatile method for the synthesis of 9-monosubstituted fluorenes under mild conditions is highly desirable.

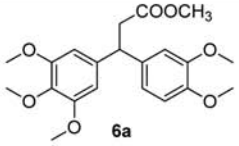
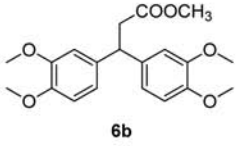
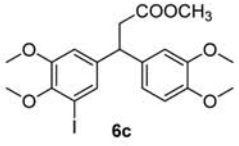
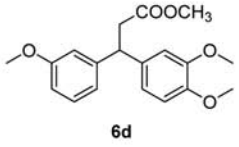
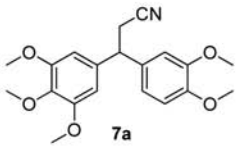
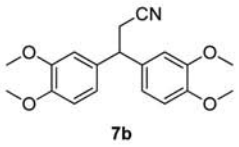
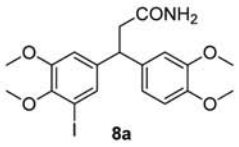
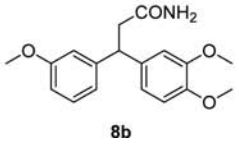
Here, we report a versatile, modular synthesis of highly functionalized 9-monosubstituted fluorenes with a Mo^{V}-mediated oxidative intramolecular coupling reaction in the key step.

Molybdenum pentachloride is a readily available molybdenum salt with an exquisite Lewis acid property.[14,15] The strong oxidative power leads to very fast transformations.[16] Therefore, many labile moieties such as amides, iodo groups, or acetals are tolerated during the coupling process.[17] The performance of the reagent can be improved by the addition of Lewis acids, e.g.

Received: January 30, 2016
Published: February 25, 2016

DOI: 10.1021/acs.orglett.6b00315
Org. Lett. 2016, 18, 1182−1185

Table 1. Overall Yield for Precursor Molecules 6−8

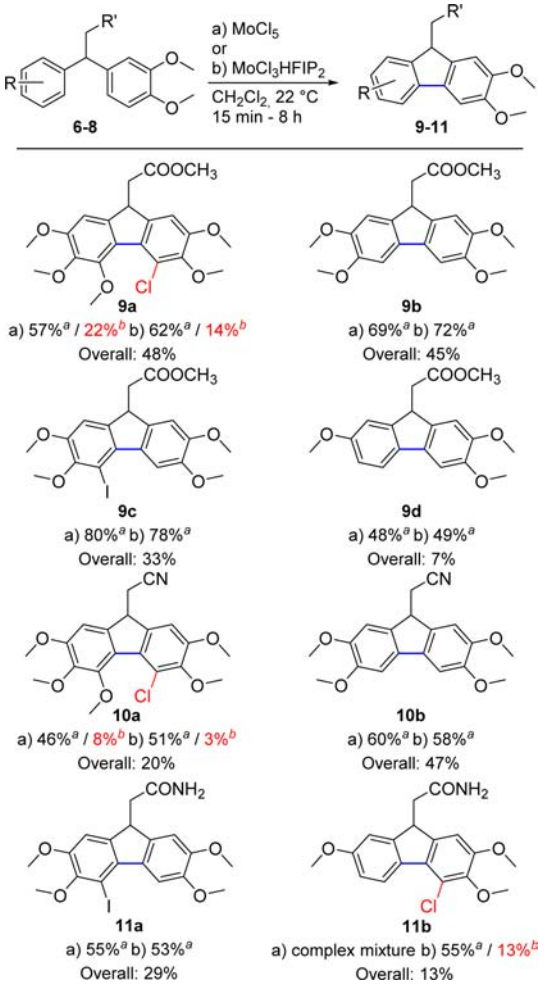
entry	route	overall yield (%)
 **6a**	A	78
 **6b**	A	63
 **6c**	A	42
 **6d**	A	13
 **7a**	B	38
 **7b**	B	62
 **8a**	B	49
 **8b**	B	23

TiCl$_4$.[18] An even more powerful Mo^V reagent was obtained by displacing two chlorido ligands by 1,1,1,3,3,3-hexafluoro-isopropanolate (HFIP). The application of this oxidizer also significantly depresses the formation of chlorinated by-products.[19] These Mo^V reagents have been previously used to construct a variety of five-, six-, seven-, and eight-membered ring systems in superior yields compared to other oxidizers such as hypervalent iodine reagents or ferric chloride.[15,20]

The diphenylpropane derivatives, which act as precursors for this oxidative coupling reaction, were synthesized via two different routes starting from the respective benzaldehydes (Scheme 1). Depending on the desired substituent in position 9 of the fluorene (see Table 2), either a Knoevenagel−Doebner condensation (route A) or a Horner−Wadsworth−Emmons reaction (route B) was performed in high yield (89−99%).[21] Subsequently, an acid catalyzed 1,4-addition of veratrole and then esterification of the acid moieties were carried out to obtain diaryl propionates **6**, diaryl propionitriles **7**, and diaryl propionic amides **8**.[22]

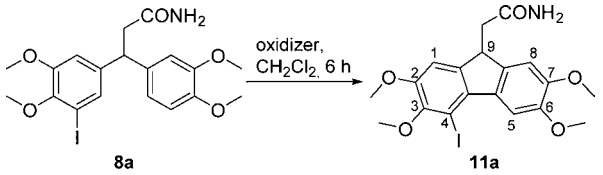
The formation of the propionic amides **8** is a result of the longer reaction times, which are required for the less electron-rich cinnamic nitriles **5c** and **5d**.[23] The lower yields of the least electron-rich derivatives **6d** and **8b** are a result of the absence of an activating methoxy group in the para position on the cinnamic acid or nitrile. The syntheses of the precursor

Scheme 2. Synthesis of Fluorene Derivatives by Oxidative Coupling



[a]Isolated yield. [b]Byproduct yield determined by ^{1}H NMR.

Table 2. Comparison of Different Oxidizers

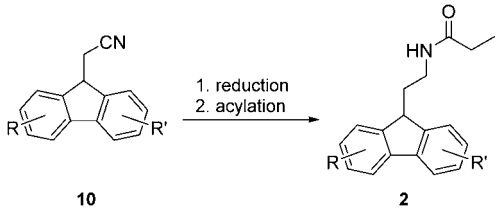


entry	oxidizer[24]	temp (°C)	yield of **11a** (%)
1	$MoCl_5$	22	55
2	$MoCl_3HFIP_2$	22	53
3	$FeCl_3$	22	13[a]
4	DDQ/H_3CSO_3H	0	0

[a]Determined by ^{1}H NMR spectroscopy.

DOI: 10.1021/acs.orglett.6b00315
Org. Lett. 2016, 18, 1182−1185

Scheme 3. Formal Conversion of the Generated Fluorenes into Bioactive Substances



molecules are reliable and easy to perform and give yields up to 78% within three steps (Table 1).

The oxidative coupling reaction was performed using two different Mo^V reagents: $MoCl_5$ and the fluoralkoxy substituted reagent $MoCl_3HFIP_2$. In position 9 of the fluorene, methoxycarbonylmethyl **9**, cyanomethyl **10**, and amides **11** are tolerated (Scheme 2). For comparable substitution patterns, the diphenyl propionates **6** lead to higher yields in the oxidative cyclization because of their less electron-withdrawing character. The C,C-coupling reaction provides the best results for precursors, which are methoxylated in the positions 3, 3′, 4, and 4′. Nevertheless, the synthesis of the fluorenes is still possible with less than four methoxy groups (**9d**, **11b**). Furthermore, even iodine moieties (**9c**, **11a**) are tolerated in the transformation. These functions are valuable leaving groups for subsequent transition metal catalysis.[10,11]

The use of the alkoxylated reagent enhances the yield for products **9a**, **10a**, and **11b**, which are prone to chlorinated byproducts (Scheme 2). Especially the least electron-rich fluorene **11b** was only accessible by using $MoCl_3HFIP_2$ instead of $MoCl_5$. The superior performance of the Mo^V reagents is underlined by comparison with other oxidation conditions. None of the other oxidizers, such as DDQ/H_3CSO_3H or $FeCl_3$, was capable of converting the iodinated substrate **8a** as effectively as the Mo^V reagents (Table 2).

The fluorenes **10** are easily convertible to *N*-(2-(fluoren-9-yl)ethyl)-propanamides by reduction of the nitrile and subsequent acylation (Scheme 3).[4] Those propanamides were reported to show chronobiotic activity similar to melatonin, which possibly results from a structure−activity relationship between fluorenylethyl amines and tryptamine derivatives.[4]

In conclusion, we have established a highly modular approach to electron-rich 9-monosubstituted fluorenes. This protocol is realiable, easy to perform and high yielding. The oxidative coupling reaction using Mo^V reagents provides superior yields compared to other oxidizers. The coupling conditions are tolerated by labile moieties, e.g. iodo groups or amides. The formation of byproducts can be successfully suppressed by the use of the alkoxylated Mo^V reagent $MoCl_3HFIP_2$. Application of this method leads to precursors to pharmacologically important fluorene derivatives **2**. The oxidative approach offers access to a wide range of highly functionalized fluorenes as building blocks for bioactive compounds and functional materials.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00315.

Experimental procedures and analytical data for all isolated intermediates and products (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the German Research Foundation DFG (WA 1276/15-1) and the Center of Innovative and Emerging Materials (CINEMA) for financial support.

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DOI: 10.1021/acs.orglett.6b00315
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