Organic LETTERS

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Access toward Fluorenone Derivatives through Solvent-Free Ruthenium Trichloride Mediated [2 + 2 + 2] Cycloadditions

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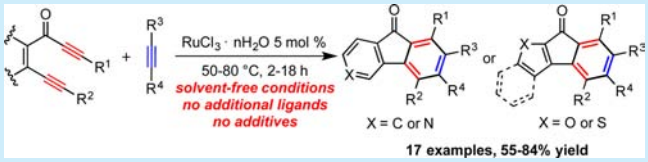
Supporting Information

ABSTRACT: An efficient and practical route for the preparation of highly substituted fluorenones and analogues via solvent-free ruthenium trichloride mediated [2 + 2 + 2] cycloaddition of α,ω-diynes and alkynes has been developed. This green chemistry approach involves a solventless and atom-economical catalytic process to generate densely functionalized fluorenones and related derivatives of high synthetic utility.



Transition-metal-catalyzed [2 + 2 + 2] cycloaddition serves as a powerful and useful method to access aromatic carbo- and heterocycles in a single step.[1] Despite the large number of metal complexes such as cobalt, nickel, rhodium, iridium, and ruthenium used for such transformations in organic solvent, the search for the development of more environmentally friendly solventless[2] [2 + 2 + 2] cycloadditions has been scarcely explored.[3]

Fluorenones and related compounds are important structural motifs found in many natural products and bioactive molecules[4] encompassing a wide range of biological, photoelectric, and electrical properties.[5] Particularly, 2,7-disubstituted amidofluorenone derivatives **A** exhibit a range of human telomerase inhibitory activities;[5c] dicationic 2-fluorenonylcarbapenems **B** were potent anti-MRS agents;[5d] indenone **C** showed anti-HIV-1 activity;[5k] compounds **D** formed ferroelectric liquid crystals,[5e] and bisindenofluorene **E** represented a novel building block class for n-type electronic materials (Figure 1).[5g] As far as transition-metal-catalyzed reactions to access fluorenones and derivatives are concerned,[6−10] several synthetic approaches based on Pd-,[6] Rh-,[7] Ag-,[8] Cu-,[9] and Re-[10]catalyzed reactions have been disclosed. Considering the growing environmental concerns,[2] we developed [2 + 2 + 2] cycloaddition reactions to approach fused functionalized arenes using eco-friendly green protocols.[11,3d,f] We report herein a practical eco-friendly straightforward route to the synthesis of highly substituted fluorenones and related compounds based on atom-economical [2 + 2 + 2] cycloadditions (Scheme 1).

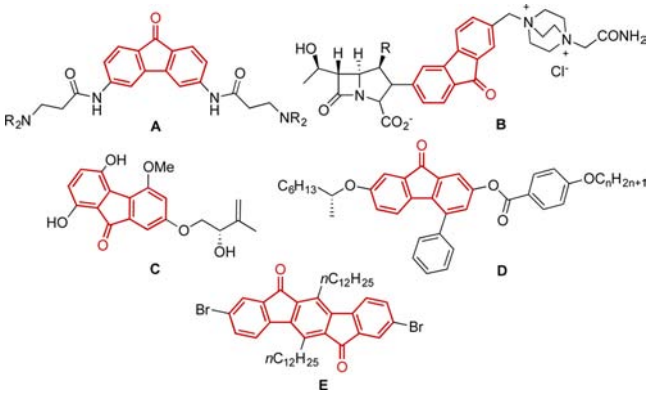
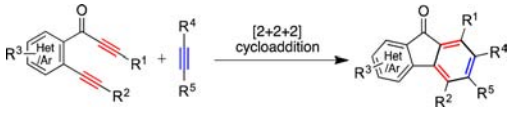


Figure 1. Examples of relevant fluorenones.

Scheme 1. Our strategy To Construct Fluorenone and Derivative Scaffolds

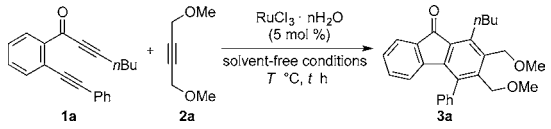


We therefore commenced our study by investigating the reaction of carbonyl-bridged α,ω-diynes **1a** with commercially available 1,4-dimethoxy-2-butyne **2a**. Ether-substituted alkynes such as **2a** were selected as partners to allow further functionalization. The reaction was first performed in the presence of $RuCl_3{\cdot}nH_2O$ (5 mol %) at 110 °C, under previously described solvent-free conditions,[3f] which generated the corresponding fluorenone **3a** (Table 1, entry 1). After checking the consumption of alkyne, we were pleased to observe that when the amount of alkyne **2a** was decreased from 6[3f] to 2 equiv, the reaction still provided the desired product **3a** in high yields (entries 1−6). Lowering the catalyst loading to 2 mol % caused a decrease of the conversion and isolated yield (entry 4, 60 and 40%, respectively). Further study showed that the reaction could be accomplished in 2 h at 50 °C, affording **3a** with a similar yield of 72% (entry 8). Moreover, the synthetic utility of this catalytic method was demonstrated by conducting the solvent-free $RuCl_3{\cdot}nH_2O$ mediated [2 + 2 + 2] cycloaddition reaction on 1 g scale under optimized conditions. Fluorenone **3a** was efficiently isolated in 71% yield.

Received: September 21, 2016
Published: October 21, 2016

DOI: 10.1021/acs.orglett.6b02840
Org. Lett. 2016, 18, 5612−5615

Table 1. Optimization of Reaction Conditions



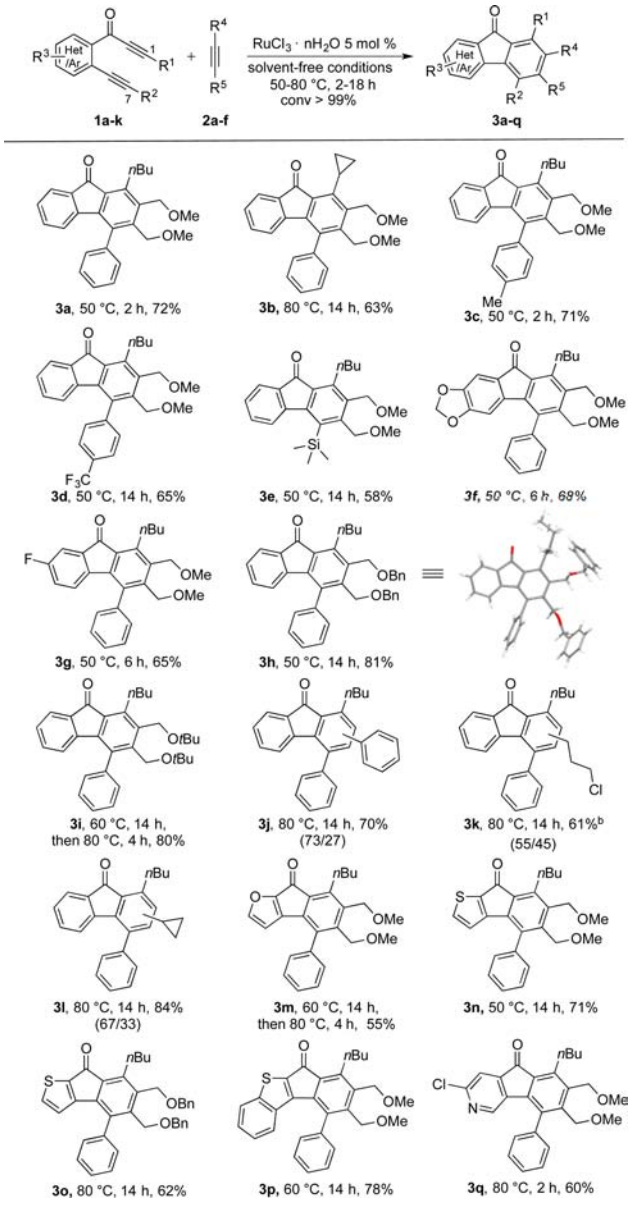
entry	1a/2a	T (°C)	t (h)	conv (%)[b]	yield (%)[c]
1	1:6	110	18	>99	86
2	1:4	80	18	>99	74
3	1:3	80	18	>99	73
4[d]	1:3	80	18	60	40
5	1:3	50	18	>99	75
6	1:2	50	18	>99	72
7	1:2	50	4	>99	73
8	1:2	50	2	>99	72[a,e]
9	1:2	50	20	>99	71[e,f]

[a]Reaction conditions: $RuCl_3{\cdot}nH_2O$ (0.0175 mmol), diyne **1a** (0.35 mmol), and alkyne **2a** (0.7 mmol) were heated in a screw-capped tube under solvent-free conditions and argon atmosphere. [b]Determined by ^1H NMR. [c]Isolated yield. [d]Using 2 mol % of $RuCl_3{\cdot}nH_2O$ (0.007 mmol). [e]Optimized reaction time. [f]One gram scale.

With a set of optimized conditions in hand, we examined the scope of the solvent-free $RuCl_3{\cdot}nH_2O$-promoted [2 + 2 + 2] cycloaddition of different substituted diynes **1a**−**g** with **2a**−**f**, as shown in Scheme 2. Switching to a cyclopropyl group on the C1 position instead of *n*-butyl promoted the formation of the corresponding adduct **3b** in 63% yield. Furthermore, both electron-donating and electron-withdrawing substituents on the phenyl ring at the C7 position, such as Me or CF_3, were tolerated and led to the expected products **3c** and **3d** in good isolated yields (65 and 71%). Rewardingly, silyl-substituted diyne **1e** was also compatible in this reaction, giving the targeted compound **3e** that constitutes an interesting scaffold for post-functionalization. To extend the scope of the reaction, we also studied the influence of the tethered phenyl group: introducing either stronger electron-rich methylenedioxy or electron-deficient fluorinated substituents gave fluorenones **3f** and **3g** in 68 and 65% yield, respectively. With regard to the alkynes, replacing the methyl group with bulkier benzyl and *tert*-butyl groups allowed the efficient preparation of the corresponding functionalized fluorenones **3h** and **3i** in high yields (81 and 80%). The structure of fluorenone **3h** was unambiguously confirmed by single-crystal X-ray diffraction analysis, as shown in Scheme 2. The cycloaddition reaction was not limited to symmetrical 1,4-dialkoxy-2-butyne because phenylacetylene, 5-chloro-1-pentyne, and cyclopropylacetylene reacted successfully, leading to inseparable mixtures of regioisomers **3j**, **3k**, and **3l** in 61−84% yield.

We next explored challenging applications of the [2 + 2 + 2] cyclization process by targeting azafluorenones, indenothiophenones, and benzo[*b*]furanones.[12−15,5m] The furanyl-, thienyl-, and aza-based fluorenones are indeed particularly interesting molecular scaffolds with biological activities such as antimicrobial, antimalarial, and DNA-damaging properties.[12] They are also key intermediates in monomers for organic materials.[13] We were pleased to find that the [2 + 2 + 2] cycloaddition reactions were effective and amenable to heterocyclic moieties as the corresponding fluorenones **3m**−**q** were obtained in good yields. The reaction of benzo[*b*]thiophene-bridged diyne afforded the suitable fused fluorenone **3p** in 78% isolated yield. The 3-aza-9-fluorenone **3q** was also cleanly obtained by using pyridine-linked

Scheme 2. Scope of Substituted Diynes and Alkynes[a]



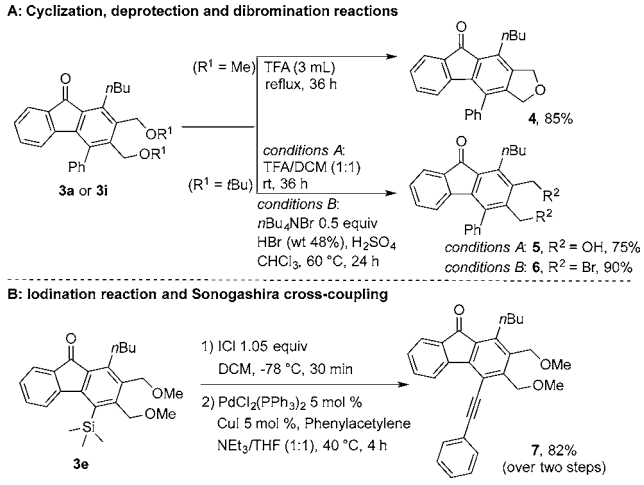
[a]Reaction conditions: $RuCl_3{\cdot}nH_2O$ (0.0175 mmol), diyne **1** (0.35 mmol), and alkyne **2** (0.7 mmol) were heated in a screw-capped tube under solvent-free conditions and argon atmosphere. The temperature was adjusted in each case for full conversion. Isolated yield. [b]Conversion = 86%.

diynes as the starting material (60% yield), with the reaction being compatible with a chlorine atom.

With several synthetically original substituted fluorenones in hand, we further investigated the benefit of such units by conducting post-functionalization reactions on ethers **3a** and **3i** and silylated derivative **3e** (Scheme 3). We anticipated that ethers **3a** and **3i** could be precursors of cyclic ethers, alcohols, or bromo derivatives.[5i] The dimethylether-substituted fluorenone **3a** was cleanly transformed to the dihydrobenzo[*b*]furan **4** in high yield (85%), in the presence of concentrated trifluoroacetic acid. Preparation of diol **5** was performed by classic deprotection of *t*-butyl-functionalized ether **3i** in 75% yield. This diol could be envisioned as a precursor of the dibrominated product **6**, a key building block for the synthesis of organic light-emitting diode

DOI: 10.1021/acs.orglett.6b02840
Org. Lett. 2016, 18, 5612−5615

Scheme 3. Post-functionalization of [2 + 2 + 2] Cycloadducts 3a, 3e, and 3i



materials.[5i] We successfully transformed directly ether **3i** to dibromide **6** in excellent yield (90%), by placing the *t*-butyl ether in a refluxing mixture of HBr and chloroform in the presence of TBAB. Considering the importance of cross-coupling reactions,[16] we carried out the iodination reaction of silyl-based fluorenone adduct **3e** and consequently the palladium-catalyzed Sonogashira cross-coupling, leading to the desired alkyne **7** in an excellent 82% yield over two steps.

To conclude, an eco-friendly straightforward approach to prepare fluorenone and related compounds is described. This solventless strategy involves a [2 + 2 + 2] cycloaddition reaction which efficiently allows the construction of complex polycyclic fluorenones, azafluorenones, benzo[*b*]furanones, and indenothiophenones in a catalytic and highly economical fashion. Furthermore, this green process using the stable and cost-effective $RuCl_3 \cdot nH_2O$ complex with neither additional ligands nor additives demonstrates practical application in laboratory scale experiments. Further challenging applications of the fluorenone derivatives and analogues are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02840.

Experimental procedures, analytical data, and NMR spectra for all compounds (PDF)
X-ray data for compound **3h** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Ministère de l'Education nationale, de l'Enseignement Supérieur et de la Recherche and the Centre National de la Recherche Scientifique. We gratefully acknowledge the China Scholarship Council for a grant to F.Y. Dr. A.K. Mandadapu (Chimie ParisTech, Paris) and G. Antola Silva (Chimie ParisTech, Paris) are acknowledged for preliminary experiments.

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DOI: 10.1021/acs.orglett.6b02840
Org. Lett. 2016, 18, 5612−5615