



Facile synthesis of perfluoroalkylated fluorenes *via* a one-pot two-step three-component process

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ABSTRACT

The efficient synthesis of perfluoroalkyl-substituted fluorenes directly from indenones, malononitrile and methyl perfluoroalk-2-ynoates *via* a one-pot two-step three-component cascade process is reported. Up to 12 examples of indenones with various substituents were converted into their corresponding functionalized fluorene derivatives in good to excellent yields.

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1. Introduction

Fluorene derivatives have attracted wide spread interest because of their important applications in the fields of biomedical and photoelectric materials^{1,2}. Moreover, they are also effective ligands in organometallic chemistry and unique protecting groups in peptide synthesis³.

As such, the development of practical and efficient methods for the synthesis of functionalized fluorenes is urgently demanded. The construction of the fluorene core most often relies on the traditional strategies, including Friedel-Crafts-type reactions⁴, transition metal-mediated cyclization⁵, radical cyclization⁶ and miscellaneous methods⁷.

Although the present methods are efficient to prepare various fluorenes, they still suffer from some limitations, such as poor accessibility of starting materials, lack of regioselectivity, limited

substrate scopes, harsh reaction conditions and tedious multistep sequences. Therefore, it is desirable to seek other general and practical strategies to quickly access structurally diversified fluorenes.

The perfluoroalkyl group is of great importance in organic and medicinal chemistry⁸, and perfluoroalkyl-substituted ring systems are synthetically available by cyclization reactions of fluorinated building blocks⁹. However, a systematic study assessing the synthesis of highly functionalized fluorenes with perfluoroalkyl group has not been, to the best of our knowledge, pursued¹⁰.

In recent years, we have reported the synthesis of various trifluoromethyl- and perfluoroalkyl-substituted heterocycle derivatives based on regioselective Michael addition of methyl perfluoroalk-2-ynoates with various nucleophiles¹¹. This strategy has been successfully applied to the synthesis of pyrroles, indoles, isoxazoles, oxazolines, thiazolines, triazoles, quinolines, chromenes and 1,5-diazepine derivatives, etc. Herein, we report, for the first time, the application of our methodology to the synthesis of various perfluoroalkyl-substituted fluorenes. The reaction proceeds smoothly under mild metal-free reaction conditions with broad functional group tolerance.

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2. Results and discussion

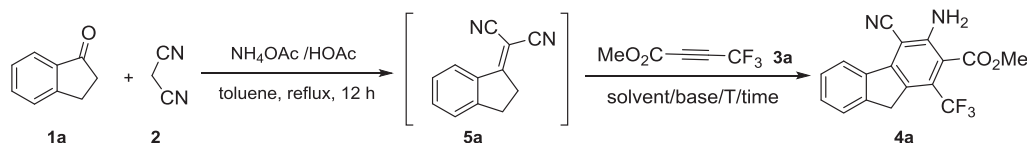
The study was commenced by investigating the reaction of commercially available 2,3-dihydro-1*H*-inden-1-one **1a**, malononitrile **2** with methyl 4,4,4-trifluorobut-2-ynoate **3a**. The reaction was carried out in one-pot two-step way. The intermediate 2-(2,3-dihydro-1*H*-inden-1-ylidene)malononitrile **5a**, generated from Knoevenagel condensation of **1a** and **2**, reacted directly with **3a** without separation in the presence of 1.0 equiv. of K₂CO₃ in toluene at 110 °C, affording the desired fluorene product **4a** in 62% yield (Table 1, entry 1). Encouraged by the above result, several key parameters including solvents, bases, the amount of base, temperature and the reaction time were screened for the second step (Table 1). Other solvents such as dichloromethane (DCM), tetrahydrofuran (THF), ethanol (EtOH), acetonitrile (MeCN), dimethyl sulfoxide (DMSO) and 1,4-dioxane were inferior to toluene in terms of reaction yields (Table 1, entry 1 vs entries 2–7). Use of 1.0 equiv. of other bases all gave inferior outcomes (Table 1, entry 1 vs entries 8–16). Also this reaction was met with little success without basic conditions (Table 1, entry 17). Taking K₂CO₃ as the suitable base, adjusting the reaction temperature from 110 to 80 °C did not significantly change the yield (Table 1, entry 1 vs entry 18). Further lowering the reaction temperature decreased the yield to 47% (Table 1, entry 19). Increasing the amount of K₂CO₃ from 1.0 to 1.5 equiv. at 80 °C proved more efficient, affording the expected product **4a** in 82% yield (Table 1, entry 21). Longer reaction time allowed however no improvement of the yield of **4a** (74%, Table 1, entry 22).

With the optimized reaction conditions in hand, the scope of this domino reaction was explored by varying the substituents (R) on the phenyl ring of indenone **1**. As shown in Table 2, indenones **1** bearing either electron-donating or -withdrawing groups were all tolerated, affording the corresponding perfluoroalkylated fluorene derivatives in good to excellent yields. Notably, replacing the substituent on the phenyl ring with halogen groups, such as fluorine, chlorine and bromine, resulted in a good yield of **4c**, **4f**, **4g**, **4h** and **4k**, respectively, which gave the chance for further functionalization through transition-metal-catalyzed reactions. It was found that the desired fluorenes could also be obtained in good yields when the substituent such as methyl group at the 4, 5, and 6 position of the phenyl ring were applied to this reaction (Table 2, entries 2, 5 and 10). Meanwhile, the pentafluoroethyl and heptafluoropropyl-substituted alkyneates could proceed smoothly and generate the desired products **4n** and **4o** in 79% and 67% yield, respectively. A single crystal of **4a** was cultivated, and the structure of **4a** was further confirmed by single-crystal X-ray analysis¹² (see Fig. 1).

On the basis of these observations, together with the related reports¹³, a plausible mechanism for our cascade annulations is illustrated in Scheme 1. Knoevenagel condensation¹⁴ of indenone **1** and malononitrile **2** took place first and generated the intermediate α,α -dicyanoolefin **5**, followed by the deprotonation to form the carbanion **6** with the base K₂CO₃.

At the second stage, the allylic anion **6** selectively attacked the more nucleophilic carbon center of the triple bond of methyl perfluoroalk-2-ynoate **3** through an intermolecular Michael addition

Table 1
Optimization of reaction conditions^a.



Entry	Solvent	Base	Temp. (°C) ^b	Time (h) ^c	Yield (%) ^d
1	Toluene	K ₂ CO ₃ (1.0)	110	6	62
2	DCM	K ₂ CO ₃ (1.0)	110	6	26
3	THF	K ₂ CO ₃ (1.0)	110	6	50
4	EtOH	K ₂ CO ₃ (1.0)	110	6	27
5	CH ₃ CN	K ₂ CO ₃ (1.0)	110	6	30
6	DMSO	K ₂ CO ₃ (1.0)	110	6	/
7	1,4-Dioxane	K ₂ CO ₃ (1.0)	110	6	47
8	Toluene	Et ₃ N (1.0)	110	6	45
9	Toluene	Piperidine (1.0)	110	6	40
10	Toluene	DIPEA (1.0)	110	6	37
11	Toluene	DABCO (1.0)	110	6	18
12	Toluene	DBU (1.0)	110	6	35
13	Toluene	Cs ₂ CO ₃ (1.0)	110	6	25
14	Toluene	KF (1.0)	110	6	46
15	Toluene	NaOH (1.0)	110	6	25
16	Toluene	K ₃ PO ₄ (1.0)	110	6	trace
17	Toluene	K ₂ CO ₃ (0)	110	6	trace
18	Toluene	K ₂ CO ₃ (1.0)	80	6	62
19	Toluene	K ₂ CO ₃ (1.0)	60	6	47
20	Toluene	K ₂ CO ₃ (0.5)	80	6	28
21	Toluene	K ₂ CO ₃ (1.5)	80	6	82
22	Toluene	K ₂ CO ₃ (1.5)	80	24	74

^a Reaction conditions: indenone **1a** (1.0 mmol), malononitrile **2** (1.0 mmol), HOAc (0.1 equiv.) and NH₄OAc (0.2 equiv.) were stirred in refluxing toluene (5 mL) for 12 h. After cooling to room temperature, K₂CO₃ (1.5 equiv.) and methyl 4,4,4-trifluorobut-2-ynoate **3a** (1.3 equiv.) were added and the mixture was stirred for another 6 h at 80 °C.

^b Reaction temperature for the second step.

^c Reaction time for the second step.

^d Isolated yields.

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