



Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet



Communication

Expedient chemoselective and catalyst-free synthesis of 3, 3-difluorochroman-4-ones from *o*-hydroxyarylenaminones and Selectfluor

Jian Xu¹, Zhijie Kuang¹, Qiuling Song*

Institute of Next Generation Matter Transformation, College of Chemical Engineering at Huaqiao University, Xiamen 361021, China

ARTICLE INFO

Article history:

Received 5 September 2017
Received in revised form 2 October 2017
Accepted 23 October 2017
Available online xxx

Keywords:

Selectfluor
o-Hydroxyarylenaminones
Catalyst-free
Chroman-4-one
Fluorination reaction
Fluorine-contained compound

ABSTRACT

An expedient and mild strategy for the synthesis of unconventional 2-(dimethylamino)-3,3-difluorochroman-4-one derivatives from *o*-hydroxyarylenaminones and Selectfluor was developed at room temperature under catalyst-free conditions. This method showed excellent chemoselectivity and great functional groups tolerance.

© 2017 Chinese Chemical Society and Institute of Materia Medica, Chinese Academy of Medical Sciences. Published by Elsevier B.V. All rights reserved.

Molecules with chroman-4-one scaffold are not only ubiquitous in natural products, but also essential nutrients for the human body [1]. Moreover, they are also widely applied in pharmaceuticals, pigments and dyes [2]. Thus, the studies of these compounds' syntheses [3] and modifications have attracted more and more attentions. A variety of bioactive molecules, which are derived from chroman-4-one, have been well applied in drugs (Fig. 1), such as the new SIRT2 inhibitor [4], flavonones [5], and GPR119 [6]. It is worthy to mention that flavonones can effectively prevent cell degeneration and delay aging process and GPR119 shows agonist activity.

Moreover, the studies of fluorine-contained compounds' synthesis have become a field of great interest and great progress has been made in fluorination reactions [7] among which Selectfluor (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)) is the most frequently used fluorination reagents. Reports about electrophilic and free radical fluorinations, which employed Selectfluor as fluorine sources, appeared frequently [8]. In 1996, Bolós's group reported the synthesis of 3-fluoro-4H-chromen-4-one from 1-fluoro-2,4,6-trimethylpyridinium triflate (NFTP), which was an expensive fluorine reagent (Scheme 1a) [9]. And in 2006, Shreeve's group

obtained 1,1-difluorinated carbonyl compounds from enamines and Selectfluor (Scheme 1b) [10]. Recently, synthesis of chromone and its derivatives from *o*-hydroxyarylenaminones had attracted considerable attention because of their simple operation and easily accessible starting materials [11]. During this manuscript preparation, Yang and coworkers reported a base promoted cyclization of *o*-hydroxyarylenaminones with Selectfluor to access 3, 3-difluorochroman-4-ones [12]. Compared with their work, there are several advantages of ours: 1) Without the additional of base, 2) more wider substrate scope including disubstituted *o*-hydroxyarylenaminone which was not accessed in yang's report, 3) lower Selectfluor loading. Therefore, we would like to report our progress on the synthesis of difluorinated chromanones with Selectfluor as a fluorine source (Scheme 1c).

Our initial studies were carried out with *o*-hydroxyarylenaminone **1a** and Selectfluor, and the mixture was stirred in toluene at room temperature for about 9 h. To our delight, the desired product 2-(dimethylamino)-3,3-difluorochroman-4-one (**2a**) was obtained in 73% yield (Table 1, entry 1). The structure of **2a** was confirmed by X-ray analysis (Fig. 2) (see Supporting information for details). When the reaction time was shortened to 3 h, the yield was almost kept untouched. To further improve the yield of **2a**, various solvents were tested (Table 1, entries 3–8). It turned out that solvent affected the reaction greatly, and non-polar solvents afforded much higher yields than polar ones. Polar solvents such as DME, CH₃CH, DMF could barely afforded any product (Table 1, entries 4–6), however, non-polar solvents such as petroleum,

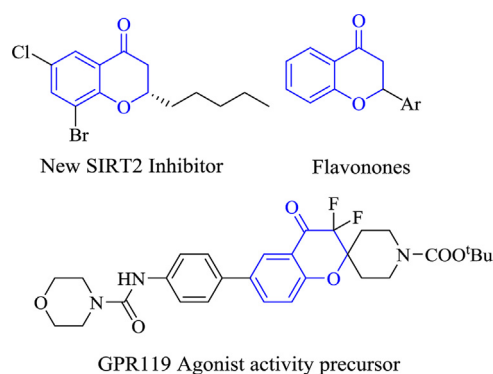
* Corresponding author.

E-mail addresses: qsong2002@gmail.com, qsong@hqu.edu.cn (Q. Song).

¹ These two authors contributed equally to this work.

<https://doi.org/10.1016/j.cclet.2017.10.027>

1001-8417/© 2017 Chinese Chemical Society and Institute of Materia Medica, Chinese Academy of Medical Sciences. Published by Elsevier B.V. All rights reserved.

**Fig. 1.** Pharmaceuticals derived from chroman-4-ones.

hexane could give **2a** in acceptable yields (Table 1, entries 7 and 8). To our delight, when cyclohexane was used as solvent, **2a** could be obtained in 85% yield (Table 1, entry 9). When the reaction time was further shortened, the yield of **2a** decreased significantly (Table 1, entries 10 and 11). Other fluorine reagent, like NFSI, was also tested in our reaction systems, unfortunately no desired product was detected (Table 1, entry 12). By far, the optimal reaction conditions were obtained as: **1a** (1.0 equiv.) and Selectfluor (2.3 equiv.) were stirred in cyclohexane (3 mL) at room temperature for 3 h. And, typical experimental procedure was below: To a 25 mL Schlenk tube, under a nitrogen atmosphere, was added 0.20 mmol of *o*-hydroxyarylenaminone (**1a**) and 0.46 mmol of Selectfluor (2.3 equiv.), then cyclohexane (3 mL) was added by syringe. The reaction mixture was stirred violently at room temperature until yellow emulsion to become clear, even colorless (3–4 h generally needed). Then, the reaction mixture was filtered by the sand core funnel. Subsequently, the filtrate was concentrated to dryness and purified by silica gel chromatography (silica gel, PE: Et₃N=50:1, v/v) to afford the product **2a** (36 mg, 78%) as a white solid.

With the optimized conditions in hand, the scope of the substrate was studied (Scheme 2). Substituents on the phenyl rings had little effect on the yields of products, either electron-withdrawing or electron-donating groups could go through the reactions smoothly, and afforded the desired products in moderate to high yields (**2a–2k**). However, the position of some substituents on the phenyl rings has a great impact on the reaction (**2j–2l**) with

Table 1
Optimization of the reaction conditions.^a

Entry	Solvent	Time (h)	Yield (%) ^b
1	Toluene	9	73
2	Toluene	3	70
3	DCM	3	31
4	DME	3	trace
5	CH ₃ CN	3	trace
6	DMF	3	trace
7	Petroleum	3	75
8	<i>n</i> -hexane	3	70
9	Cyclohexane	3	85(78) ^c
10	Cyclohexane	2	51
11	Cyclohexane	1	41
12 ^d	Cyclohexane	3	trace

^a all the reactions were carried out with **1a** (1.0 equiv.), Selectfluor (2.3 equiv.) in solvent (3 mL) under room temperature.

^b Determined by GC.

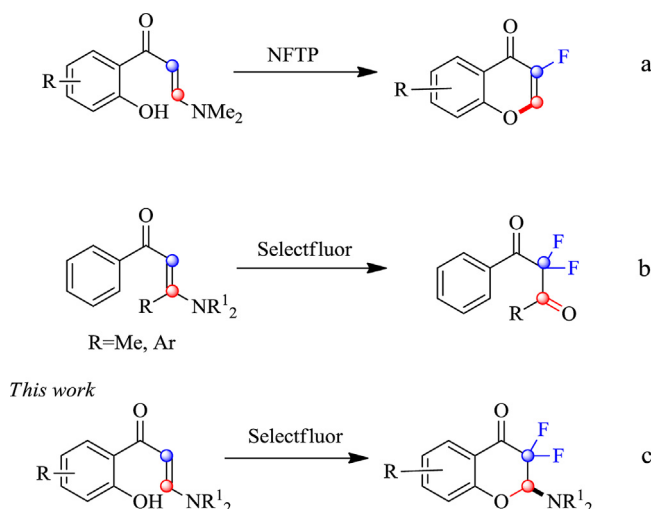
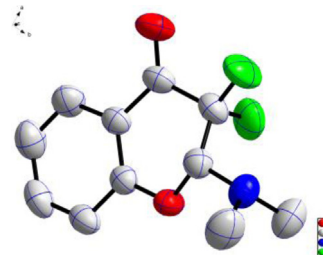
^c Isolated yield.

^d *N*-Fluorobenzenesulfonimide (2.3 equiv.) was used.

the *ortho* one giving the lowest yield, and the steric hindrance might be the direct cause of the low yield of **2l**. Polycyclic substrates could also go through the cyclization and difluorination process smoothly rendering **2m** in 59% yield, and **2n** in 92% yield. Interestingly, when vinyl and alkynyl groups were placed on the phenyl rings of the substrates, the desired products were also successfully obtained (**2o–2r**). It's worthy to note that both terminal and internal unsaturated carbon-carbon bonds were well compatible. Heterocyclic substituents, such as 3-thienyl, 2-thienyl and 2-furyl, were also tolerated well under our reaction systems, and the desired products were obtained in good to excellent yields (**2s–2u**). The substituents on the nitrogen atom were also tested (**2v, 2w**). When *N, N*-dimethyl group was replaced with pyrrolidinyl, the corresponding product **2v** was obtained in 95% yield, which was much higher than the yield of **2a**. However, when replaced with diisopropyl, the yield of **2w** was decreased a little compared with **2a**. At last, when large steric hindered substrate **1x** was applied, the desired product **2x** was only afforded in 23% yield.

Large scale experiment was also carried out with **1a** (5 mmol) and Selectfluor (11.5 mmol) under our standard reaction conditions (Scheme 3). The reaction was completed in 6 h with 70% of **2a**.

To gain a better understanding of the reaction process, several control experiments were conducted (Scheme 4). When the reaction was carried out in the presence of TMEPO (2.3 equiv.) under our standard conditions, difluorinated product **2a** could still be isolated in 45% yield (Scheme 4a). Thus, we considered that the

**Scheme 1.** Reactions of fluorine reagents with arylenaminones.**Fig. 2.** The X-ray crystallography of **2a**.

Download English Version:

<https://daneshyari.com/en/article/7693442>

Download Persian Version:

<https://daneshyari.com/article/7693442>

[Daneshyari.com](https://daneshyari.com)