ORGANIC PROCESS RESEARCH & DEVELOPMENT
OPR&D

Full Paper

A Two-Step, One-Pot and Multigram-Scale Synthesis of N-Difluoromethylthiophthalimide

Dianhu Zhu, Xin Hong, Dezhi Li, Long Lu, and Qilong Shen

Org. Process Res. Dev., **Just Accepted Manuscript** • DOI: 10.1021/acs.oprd.7b00203 • Publication Date (Web): 07 Jul 2017

A Two-Step, One-Pot and Multigram-Scale Synthesis of *N*-Difluoromethylthiophthalimide

Dianhu Zhu, Xin Hong, Dezhi Li, Long Lu and Qilong Shen**

Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, University of Chinese Academy Sciences, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, P. R. China

ABSTRACT. A new method for the 100 gram-scale synthesis of *N*-difluoromethylthiophthalimide **1** from cheap commodity chemical benzyl mercaptan and HCF_2Cl or other difluorocarbene precursors was described. Reagent **1** is an excellent electrophilic difluoromethylthiolating reagent as demonstrated by the gram-scale synthesis of five difluoromethylthiolated derivatives of structurally complicated drug-like molecules and natural products.

Keywords: Fluorine, Difluoromethylthio, gram-scale, electrophilic

Introduction

Recently, the difluoromethylthio group ($-SCF_2H$) has attracted a particular attention from both academia and industry, mainly due to its intrinsic beneficial properties that can be utilized to improve the lead compound's efficacy including lipophilicity and metabolic stability.[1] It is also known that the difluoromethylthio group is less electron-withdrawing, less lipophilic ($\pi_R = 0.68$),

and less stable to the basic conditions than its analog-the trifluoromethylthio group (-SCF_3).[2] These characteristics of the difluoromethylthio group can be advantageous because it provides an opportunity for the medicinal chemists to fine-tune the molecule's pharmacokinetics by judiciously decorating it with either a CF_3S group or a HCF_2S group. In addition, the difluoromethylthiolated compounds are superior in the system that requires a short-lived metabolite than the trifluoromethylthiolated analogs.[3] Furthermore, as a weak hydrogen-bonding donor, the difluoromethylthio group may serve as a bio-isostere to OH or SH group, thus enhancing the compound's binding affinity toward the target protein.[4] Thus, not surprisingly, several drugs and agrochemicals containing the difluoromethylthio group including β-lactamase-resistant oxcephalosporin antibiotic Flomoxef sodium,[5] pesticide Pyriprole[6] and broad-spectrum paddy herbicide Pyrimisulfan[7] have already been on the market (Fig. 1).

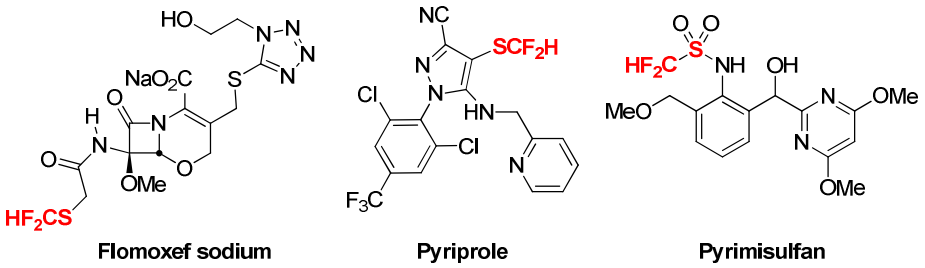


Figure 1. Drugs and agrochemicals containing a difluoromethylthio group. Reproduced from reference 10. Copyright 2015 American Chemical Society.

Several methods have been reported for the preparation of difluoromethylthiolated compounds that typically involves nucleophilic attack of an *in situ* formed difluoromethyl carbene intermediate or an electrophilic difluoromethyl reagent by an appropriate thiolate.[8-9] Yet, these classic methods require the preformation of thiols, which might constitute a challenging task for more complicated molecules. To overcome this shortcoming, in 2015, we invented the first shelf-stable electrophilic difluoromethylthiolating reagent-*N*-difluoromethylthiophthalimide **1**,[10] which reacted with a wide range of nucleophiles including aryl/vinyl boronic acids, alkynes,

β-ketoesters, oxindoles and electron-rich heteroarenes such as indole, pyrrole, 1*H*-pyrrolo[2,3-b]pyridine, imidazo[1,2-a]pyridine, aminothiazole, isoxazole and pyrazole, and heteronucleophiles such as amines and thiols under mild conditions. The excellent functional group tolerance in these reactions makes reagent **1** the choice for the preparation of more complicated, densely functional drug-like molecules. However, there is one limitation of reagent **1** that hampered its further widespread applications. Its preparation required a stoichiometric amount of $[(SIPr)Ag(CF_2H)]$[11] (SIPr = 1,3-bis(2,6-diisopropylphenyl)imidazolin-2-ylidene), which make reagent **1** rather expensive since silver is one of the precious metals. Herein, we report an alternative two-step, one-pot route for the 100 g-scale preparation of reagent **1** from easily available benzyl difluoromethylthioether **1a**. This synthetic method for the preparation of reagent **1** circumvents the use of silver complex, making it easy for scale-up and warranting its widespread applications in the future.

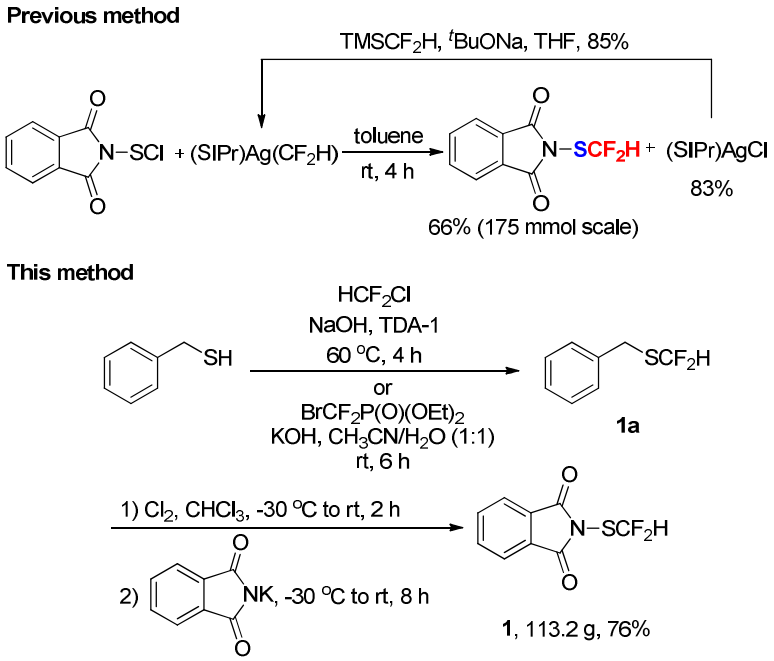


Figure 2. The synthesis of *N*-difluoromethylthiophthalimide.

Results and Discussion

Synthesis of *N*-difluoromethylthiophthalimide 1. The starting material benzyl difluoromethylthioether **1a** was prepared by reaction of benzyl mercaptan with HCF_2Cl (R22)[12] or bromodifluoromethanephosphonate[13] under basic conditions, according to the reported procedures. As shown in Figure 2, treatment of benzyl difluoromethylthioether **1a** with a solution of Cl_2 in $CHCl_3$ at room temperature for 2 h, followed by the addition of potassium phthalimide gave desired ***N*-difluoromethylthiophthalimide 1**. Presumably, difluoromethylthioether **1a** reacted with chlorine to generate a highly reactive intermediate HCF_2SCl, which was observed by ^{19}F NMR spectroscopy with a chemical shift at -97.2 ppm. The *in situ* formed HCF_2SCl then reacted with potassium phthalimide gave the *N*-difluoromethylthiophthalimide **1** in high yield. Even though the toxicity of HCF_2SCl has not been reported, its analog CF_3SCl was known to be highly toxic.[14] Thus, the one-pot procedure that avoiding the isolation of HCF_2SCl is highly desirable.

During the development of the procedure for the preparation of *N*-difluoromethylthiophthalimide **1**, we noticed that the way how chlorine was added to the solution of benzyl difluoromethylthioether **1a** was crucial for the high yielding formation of reagent **1**. When chlorine gas was bubbled into the solution of difluoromethylthioether **1a** in a reaction vessel which was connected to an oil bubbler, the reaction was messy and the yield for the formation of reagent **1** was low, as determined by ^{19}F NMR spectroscopy. It was reasoned that the chlorine bubbles blow away the volatile HCF_2SCl (b.p. 25-35 ^oC).[15] Consequently, the yield of the desired reagent **1** decreased significantly. Secondary, we also found that the yield of reagent **1** decreased when excess chlorine gas was used. It is likely that excess chlorine would react with reagent **1** to from intermediate HCF_2SCl and a byproduct *N*-chlorophthalimide, which was difficult to be separated from reagent **1**. Thus, to maximize the yield for the formation of

reagent **1**, an aliquot was withdrawn from the reaction vessel from time to time. An internal standard (trifluorotoluene) was added and the conversion of the starting material benzyl difluoromethylthioether **1a** was then determined by ^{19}F NMR spectroscopy. Accordingly, a stoichiometric amount of chlorine solution in $CHCl_3$ was added and the mixture was allowed to react at room temperature for 2 h before an excess amount of potassium phthalimide (1.2 equiv.) was added to ensure the full conversion of the intermediate to generate the desired product.

We also found that the solvent has a great influence on the yield of reagent **1**, as shown in Table 1. When the reaction was conducted in $CHCl_3$, a high yield of 78% was observed, while the yield decreased to 63% when chlorobenzene was used as the solvent. More strikingly, formation of the reagent was observed in less than 10% yields when the same reaction was conducted in toluene or acetonitrile. Under the optimized reaction conditions, 113 g of *N*-difluoromethylthiophthalimide **1** was isolated after a simple recrystallization when 120 g of difluoromethylthioether **1a** was reacted with 650 mL of chlorine solution in $CHCl_3$ (1.0 M) and then further treated with 145 g of potassium phthalimide.

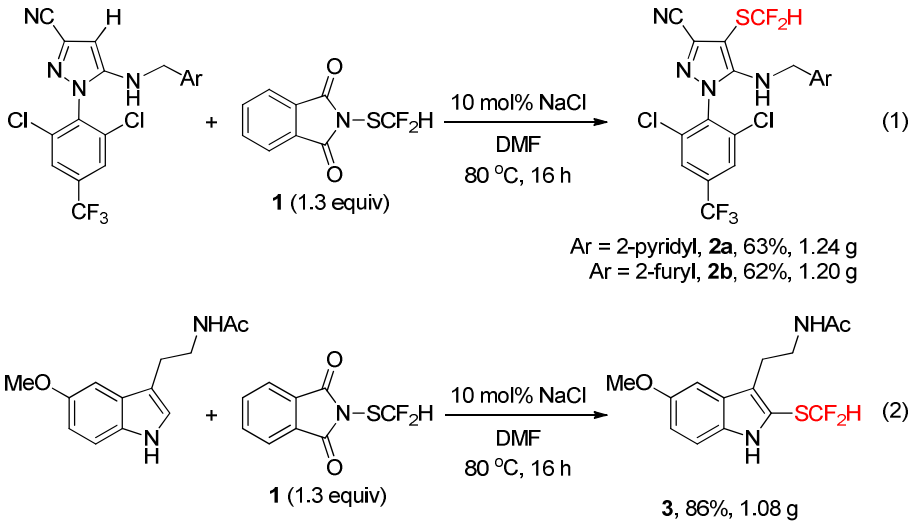
Table 1. The effects of the Cl_2/solvent solution of the reaction.[a]

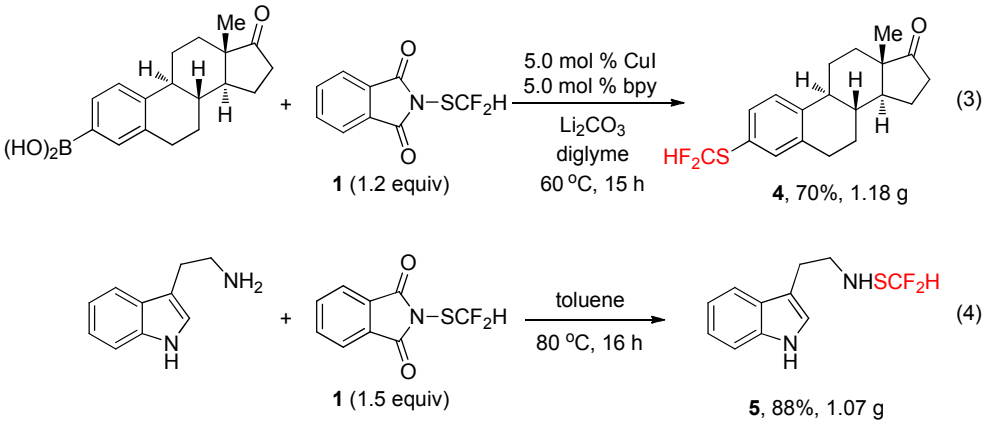
entry	solvent	yield (%)[a]
1	$CHCl_3$	78%
2	PhCl	63%
3	toluene	<10%
4	CH_3CN	<10%

[a]Yields were determined by ^{19}F NMR analysis of the crude reaction mixture with $PhCF_3$ as an internal standard.

Reactions of *N*-difluoromethylthiophthalimide 1. With the new method for the 100 g-scale synthesis of reagent **1** in hand, we next explored its applications by synthesizing difluoromethylthiolated derivatives of a few drug, agrochemical molecules or natural products on gram-scale, as summarized in Scheme 1.

Pyriprole,[16] a classic insecticide with a comparable efficacy with other modern insecticidal active ingredients such as fipronil, imidacloprid, spinetoram or spinosad, is highly effective against fleas and several tick species. It was found that in the presence of 10 mol% NaCl, pyriprole precursor reacted efficiently with reagent **1** to give pyriprole in 63% yield on gram-scale (Scheme 1, Eq. 1).[17] Likewise, its furyl-substituted analog was also synthesized in 62% yield (Scheme 1, Eq. 1). Furthermore, Melatonine,[18] a hormone from the pineal gland that regulates sleep and wakefulness, reacted with reagent **1** in the presence of 10 mol% NaCl to give the corresponding difluoromethylthiolated malatonine derivative in 86% yield (Scheme 1, Eq. 2). We also found that in the presence of a copper catalyst, boronic acid derivative of natural product estrone was able to be difluoromethylthiolated in 70% yield (Scheme 1, Eq. 3). Finally, it was found that tryptamine could react smoothly with reagent **1** in toluene in the absence of any transition-metal catalyst to afford the corresponding difluoromethylthiolated tryptamine in high yields (Scheme 1, Eq. 4).





Scheme 1. Preparation of difluoromethylthiolated derivatives of a few drug, agrochemical molecules or natural products on gram-scale.

Conclusion

In summary, a new and simple synthetic method of *N*-difluoromethylthiophthalimide **1** on a hundred gram-scale has been developed. Reagent **1** can be efficiently synthesized in three steps from cheap commodity chemical benzyl mercaptan and HCF_2Cl or other difluorocarbene precursors. *N*-difluoromethylthiophthalimide **1** is an excellent electrophilic difluoromethylthiolating reagent as demonstrated by the gram-scale synthesis of five difluoromethylthiolated derivatives of structurally complicated drug-like molecules and natural products. Thus, the method developed for 100 gram-scale synthesis of *N*-difluoromethylthiophthalimide **1** open a door for its further applications and should contribute to the development of drug or agrochemicals bearing the difluoromethylthio group in the future.

Experimental Section

General procedure for the synthesis of difluorobenzyl thioether. *n*-Hexane (3.0 L) was placed into three-neck round bottom flask equipped with a stirring bar under the cold bath (-78

°C) and chlorodifluoromethane (R-22, 1.5 mol) was bubbled slowly. Sodium hydroxide (100 g, 2.50 mol), tris(2-(2-methoxyethoxy)ethyl)amine (TDA-1, 16.2 g, 50.0 mmol) and benzyl mercaptan (124 g, 1.00 mol) were added. The reaction was stirred at 60 °C for 2-4 h under the dry ice-acetone condensation. The resulting precipitate was filtered and the filtrate was evaporated in vacuo. The residue was purified by flash chromatography on silica gel to give difluorobenzyl thioether as light pink oil (106 g, 61%).

Alternatively, potassium hydroxide (168 g, 3.00 mol), acetonitrile/H_2O (1400 mL，1:1）and benzyl mercaptan (18.6 g, 150 mmol) were placed into three round bottom flask equipped with a stirring bar. The mixture was cooled to -78 °C and diethyl bromodifluoromethanephosphonate[19] (80.1 g, 300 mmol) were added. The reaction was stirred at room temperature for 4-6 h. Et_2O (2.0 L) was added and the organic phase was separated. The aqueous phase was extracted with Et_2O (400 mL × 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel to give difluorobenzyl thioether as light pink oil (22.5 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$, 293 K, TMS) δ 7.35 (s, 2 H), 7.34 (t, J = 1.2 Hz, 2 H), 7.27-7.30 (m, 1 H), 6.73 (t, J = 56.0 Hz, 1 H); 4.02 (s, 2 H); ^{19}F NMR (375 MHz, $CDCl_3$) δ -94.4 (d, J = 56.2 Hz, 2 F); ^{13}C NMR (125 MHz, $CDCl_3$, 293 K, TMS) δ 136.2, 128.9, 128.8, 127.6, 120.2 (t, J = 271.2 Hz), 31.8 ppm.

General procedure for the synthesis of *N*-difluoromethylthiophthalimide 1. Into a 2.0 L Shlenk tube was added dry $CHCl_3$ (1.5 L) and get weighed. Chlorine gas was bubbled slowly for 15 min. The Shlenk tube was weighed again to get the amount of chlorine gas in $CHCl_3$. The concentration of Cl_2 in $CHCl_3$ was then calculated. An aliquot of Cl_2 in $CHCl_3$ (650 mL, 1.0 M) was added with 850 mL of $CHCl_3$ in a 2.0 L three-neck round bottom flask. The mixture was cooled to -30 °C in the dark and $BnSCF_2H$ (120.4 g, 650 mmol) was added slowly over a period

of 30 min. The mixture was warmed to 23 °C and the mixture was further stirred for 2 hours. The mixture was then cooled to -30 °C and potassium phthalimide (144.5 g, 1.2 equiv, 780 mmol) was added in three times. The temperature was then warmed to 23 °C and the reaction was further stirred at room temperature for 8 hours. The mixture was filtered through a layer of Celite and washed with CH_2Cl_2 (200 mL × 3). The solvent was evaporated in *vacuo* and the residue was purified by recrystallization from CH_2Cl_2/petroleum ether to give *N*-(difluoromethylthio)phthalimide as a white solid (113.2 g, 76%).

General procedure for difluoromethylthiolation of heteroarenes with *N*-(difluoromethylthio)phthalimide 1. Heteroarene (4.0 mmol), *N*-(difluoromethylthio)phthalimide **1** (5.2 mmol) and NaCl (0.4 mmol) were placed into an oven-dried Schlenk tube that was equipped with a stirring bar under argon. Freshly distilled DMF (20.0 mL) was added. The reaction was stirred at 80 ^{o}C for 16 h. Distilled water (100.0 mL) and diethyl ether (400.0 mL) was added and the organic phase was separated. The aqueous phase was extracted with diethyl ether (80.0 mL × 3). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The residue was purified by flash chromatography on silica gel to give the difluoromethylthiolated heteroarene. **1-(2,6-Dichloro-4-(trifluoromethyl)phenyl)-4-((difluoro-methyl)thio)-5-((pyridin-2-ylmethyl)amino)-1*H*-pyrazole-3-carbonitrile 2a**. 1.24 g, 63%. ^{1}H NMR (400 MHz, $CDCl_3$, 293 K, TMS) δ 8.38 (d, *J* = 8.0 Hz, 1 H), 7.73 (s, 2 H), 7.64 (t, *J* = 8.0 Hz, 1 H), 7.17 (t, *J* = 8.0 Hz, 2 H), 6.70 (t, *J* = 56.0 Hz, 1 H), 5.92 (t, *J* = 8.0 Hz, 1 H), 4.55 (d, *J* = 4.0 Hz, 2 H); ^{19}F NMR (375 MHz, $CDCl_3$) δ -63.27 (s, 3 F), -93.3 (d, *J* = 56.2 Hz, 2 F); ^{13}C NMR (125 MHz, $CDCl_3$, 293 K, TMS) δ 154.8, 152.0, 148.8, 136.9, 136.7, 135.8, 134.5 (q, *J* = 33.6 Hz), 134.2, 126.2 (q, *J* = 3.75 Hz), 123.4,

122.7, 121.9 (q, J = 272.5 Hz), 121.5, 121.4, 119.2 (t, J = 277.4 Hz), 112.0, 85.4 (t, J = 3.75 Hz), 48.0 ppm.

1-(2,6-Dichloro-4-(trifluoromethyl)phenyl)-4-((difluoromethyl)thio)-5-((furan-2-yl-methyl) amino)-1*H*-pyrazole-3-carbonitrile 2b. 1.20 g, 62%. ^{1}H NMR (400 MHz, $CDCl_3$, 293 K, TMS) δ 7.75 (s, 2 H), 7.27 (d, J = 4.0 Hz, 1 H), 6.65 (t, J = 56.0 Hz, 1 H), 6.26-6.27 (q, J = 4.0 Hz, 1 H), 6.13 (d, J = 4.0 Hz, 1 H), 4.37 (s, 1 H), 4.37 (s, 2 H); ^{19}F NMR (375 MHz, $CDCl_3$) δ -63.32 (s, 3 F), -92.8 (d, J = 56.2 Hz, 2 F); ^{13}C NMR (125 MHz, $CDCl_3$, 293 K, TMS) δ 151.6, 150.2, 142.7, 136.7, 136.5, 135.7, 134.7 (q, J = 33.6 Hz), 134.1, 126.3 (q, J = 3.75 Hz), 121.9 (t, J = 272.5 Hz), 119.1 (t, J = 276.2 Hz), 111.8, 110.5, 108.2, 108.0, 87.2 (t, J = 3.75 Hz), 41.8 ppm.

***N*-(2-(2-((Difluoromethyl)thio)-5-methoxy-1*H*-indol-3-yl)ethyl)acetamide 3**. 1.08 g, 86%. ^{1}H NMR (400 MHz, $CDCl_3$, 293 K, TMS) δ 8.69 (s, 1 H), 7.24 (d, J = 8.0 Hz, 1 H), 7.04 (d, J = 4.0 Hz, 1 H), 6.91 (dd, J = 8.0, 4.0 Hz, 1 H), 6.71 (t, J = 56.0 Hz, 1 H), 5.70 (s, 1 H), 3.82 (s, 3 H), 3.54 (q, J = 8.0 Hz, 2 H), 3.06 (t, J = 8.0 Hz, 2 H), 1.90 (s, 3 H); ^{19}F NMR (375 MHz, $CDCl_3$) δ -91.0 (d, J = 56.2 Hz, 2 F); ^{13}C NMR (125 MHz, $CDCl_3$, 293 K, TMS) δ 170.4, 154.4, 132.7, 127.7, 122.1, 119.8 (t, J = 277.5 Hz), 115.6 (t, J = 2.50 Hz), 115.2, 112.2, 100.4, 55.8, 39.9, 24.8, 23.3 ppm.

General procedure for difluoromethylthiolation of aryl boronic acids with *N*-(difluoromethylthio)phthalimide 1. Boronic acid derivative of estrone (1.49 g, 5.00 mmol), *N*-(difluoromethylthio)phthalimide **1** (1.4 g, 6.0 mmol), Li_2CO_3 (128 mg, 2.50 mmol), CuI (0.25 mmol, 0.05 equiv), 2,2'-bipyridine (39 mg, 0.25 mmol) were placed into an oven-dried Schlenk tube that was equipped with a stirring bar under argon. Freshly distilled diglyme (30.0 mL) was added and the mixture was stirred at 60 ^{o}C for 15 h. Distilled water (100.0 mL) and Et_2O (400.0 mL) was added and the organic phase was separated. The aqueous phase was extracted with Et_2O

(3×80.0 mL). The combined organic extracts were washed with 80 mL of distilled water, dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The product was purified by flash chromatography on silica gel to give the difluoromethylthiolated estrone (1.18 g, 70%). **(8R,9S,13S,14S)-3-((Difluoromethyl)thio)-13-methyl-7,8,9,11,12,13,15,16-octahydro-6*H*-cyclopenta[a]phenanthren-17(14H)-one 4**. ^{1}H NMR (400 MHz, $CDCl_3$, 293 K, TMS) δ 7.24-7.34 (m, 3 H), 6.78 (t, *J* = 56.0 Hz, 1 H), 2.91 (t, *J* = 4.0, 2 H), 2.50 (q, *J* = 8.0, 1 H), 2.40 (m, 1 H), 2.29 (m, 1 H), 1.93-2.18 (m, 4 H), 1.38-1.67 (m, 6 H), 0.89 (s, 3 H); ^{19}F NMR (375 MHz, $CDCl_3$) δ -91.4 (d, *J* = 56.2 Hz, 2 F); ^{13}C NMR (125 MHz, $CDCl_3$, 293 K, TMS) δ 220.47, 141.86, 137.98, 135.85, 132.62, 126.46, 122.89 (t, *J* = 2.5 Hz), 121.15 (t, *J* = 273.7 Hz), 50.48, 47.89, 44.32, 37.84, 35.80, 31.53, 29.15, 26.23, 25.57, 21.57, 13.81 ppm.

General procedure for difluoromethylthiolation of tryptamine with *N*-(difluoromethylthio)phthalimide 1. A Shlenk tube charged with tryptamine (0.80 g, 5.0 mmol) and *N*-(difluoromethylthio) phthalimide **1** (1.7 g, 7.5 mmol) was added toluene (30.0 mL). The mixture was stirred at 80 ^{o}C for 16 h. The solvent was removed under vacuum and the residue was purified by flask column chromatography to give difluoromethylthiolated tryptamine (1.07, 88%). ***N*-(2-(1*H*-Indol-3-yl)ethyl)-*S*-(difluoromethyl)thiohydroxylamine 5**. ^{1}H NMR (400 MHz, $CDCl_3$, 293 K, TMS) δ 8.01 (s, 1 H), 7.61 (d, *J* = 8.0 Hz, 1 H), 7.36 (d, *J* = 8.0 Hz, 1 H), 7.22 (td, *J* = 8.0, 0.8 Hz, 1 H), 7.14 (td, *J* = 8.0, 0.8 Hz, 1 H), 7.01 (d, *J* = 2.0 Hz, 1 H), 6.61 (t, *J* = 56.0 Hz, 1 H), 3.35 (q, *J* = 8.0, 2 H), 2.99 (t, *J* = 8.0, 2 H), 2.73 (s, 1 H); ^{19}F NMR (375 MHz, $CDCl_3$) δ -100.3 (d, *J* = 56.2 Hz, 2 F); ^{13}C NMR (100.7 MHz, $CDCl_3$, 293 K, TMS) δ 136.3, 127.3, 123.2 (t, *J* = 275.9 Hz), 122.2 (d, *J* = 1.0 Hz), 120.4, 119.5, 118.7, 112.7, 111.3, 54.0, 26.4 ppm.

Supporting Information. NMR data of compound **1-5**. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*Email: lulong@sioc.ac.cn; shenql@sioc.ac.cn

Notes

A provisional patent (application No. CN201610469651.4) about the preparation of *N*-difluoromethylthiophthalimide **1** was filed by Shanghai Institute of Organic Chemistry.

ACKNOWLEDGMENT

The authors gratefully acknowledge the financial support from National Natural Science Foundation of China (21625206, 21632009, 21372247, 21572258, 21421002) and the Strategic Priority Research Program of the Chinese Academy of Sciences (XDB20000000) for financial support.

REFERENCES

1. a) Manteau, B.; Pazenok, S.; Vors, J.-P.; Leroux, F. R. *J. Fluorine Chem.* **2010**, *131*, 140; b) Xu, X.-H.; Matsuzaki, K.; Shibata, N. *Chem. Rev.* **2015**, *115*, 731; c) Ni, C.-F.; Hu, M.-Y.; Hu, J.-B. *Chem. Rev.* **2015**, *115*, 765; d) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359; e) Meanwell, N. A. *J. Med. Chem.* **2011**, *54*, 2529; f) Xiong, H.-Y.; Pannecoucke, X.; Besset, T. *Chem. Eur. J.* **2016**, *22*, 16734.

2. a) Rico, I.; Wakselman, C. *Tetrahedron Lett.* **1981**, *22*, 323; b) Fujita, T.; Iwasa, J.; Hansch, C. *J. Am. Chem. Soc.* **1964**, *66*, 5175.

3. Langlois, B. R. *J. Fluorine Chem*. **1988**, *41*, 247.

4. a) Erickson, J. A.; McLoughlin, J. I. *J. Org. Chem.* **1995**, *60*, 1626; b) Narjes, F.; Koehler, K. F.; Koch, U.; Gerlach, B.; Colarusso, S.; Steinkühler, C.; Brunetti, M.; Sergio Altamura, S.; De Francesco, R.; Matassa, V. G. Bioorg. *Med. Chem. Lett.* **2002**, *1*2, 701; 3) Xu, Y.; Prestwich, G. D. *J. Org. Chem.* **2002**, *67*, 7158.

5. a) Shimizu, K. *Jpn J. Antibiot.* **1988**, *12*, 1809; b) Ito, M.; Ishigami, T. *Infection*, **1991**, *19*, S253.

6. Fourie, J. J.; Horak, I. G. Puente Redondo, V de la *Vet. Rec.* **2010**, *167*, 442.

7. Yoshimura, T.; Nakatani, M.; Asakura, S.; Hanai, R.; Hiraoka, M.; Kuwahara, S. *J. Pest. Sci.* **2011**, **36**, 212.

8. Reviews for difluoromethylation of thiolates: a) Brahms, D. L. S.; Dailey, W. P. *Chem. Rev.* **1996**, *96*, 1585**;** b) Tozer, M. J.; Herpin, T. F. *Tetrahedron* **1996**, *52*, 8619; c) Hu, J.-B.; Zhang, W.; Wang, F. *Chem. Commun.* **2009**, 7465.

9. Selected recent methods for preparation of difluoromethylated compounds: a) W. Zhang, J.-M. Zhu, J.-B. Hu, *Tetrahedron Lett.* **2008**, *49*, 5006; b) G. K. Surya Prakash, Z. Zhang, F. Wang, C.-F. Ni, G. A. Olah, *J. Fluorine Chem.* **2011**, *13*2, 792; c) Fujiwara, Y.; Dixon, J. A.; Rodriguez, R. A.; Baxter, R. D.; Dix-on, D. D.; Collin, M. R.; Blackmond, D. G.; Baran, P. S. *J. Am. Chem. Soc.* **2012**, *134*, 1494; d) Li, L.-C.; Wang, F.; Ni, C.-F.; Hu, J.-B. *Angew. Chem. Int. Ed.* **2013**, *52*, 12390; e) Bayarmagnai, B.; Matheis, C.; Jouvin, K.; Goossen, L. J. *Angew. Chem. Int. Ed.* **2015**, *54*, 5753; f) Wu, J.; Gu, Y.; Leng, X.-B.; Shen, Q. *Angew. Chem. Int. Ed.* **2015**, *54*, 7648; g) Wu, J.; Liu, Y.-F.; Lu, C.-H.; Shen, Q. *Chem. Sci.* **2016**, *7*, 3757; h) Arimori, S.; Matsubara, O.; Takada, M.; Shiro, M.; Shibata, N. *R. Soc. Open Sci.* **2016**, *3*:160102; i) J.-B. Han, H.-L. Qin, S.-H. Ye, L. Zhu, C.-P. Zhang, *J. Org. Chem.* **2016**, *81*, 2506; j) Y.-M. Lin, W.-B. Yi, W.-Z.

Shen, G.-P. Lu, *Org. Lett.* **2016**, *18*, 592.; k) J. L. Howard, C. Schotten, S. T. Alston, D. L. Browne, *Chem. Commun.* **2016**, *52*, 8448; l) Zhao, X.; Wei, A.; Li, T.; Su, Z.; Chen, J.; Lu, K. *Org. Chem Front.* **2017**, *4*, 232; m) Zhao, X.; Li, T.-J.; Yang, B.; Qiu, D.; Lu, K. *Tetrahedron* **2017**, *73*, 3112; n) Huang, Z.-Y.; Matsubara, O.; Jia, S.C.; Tokunaga, E.; Shibata, N. *Org. Lett.* **2017**, *19*, 934; o) Yan, Q.; Jiang, L.-Q.; Yi, W.-B.; Liu, Q.-R.; Zhang, W. *Adv. Synth. Catal.* **2017**, asap, doi: 10.1002/adsc.201700270.

10. a) Zhu, D.-H.; Gu, Y.; Lu, L.; Shen, Q. *J. Am. Chem. Soc.* **2015**, *137*, 10547.

11. a) Gu, Y.; Leng, X.-B.; Shen, Q. *Nat. Commun.* **2014**, *5*, 5405, doi: 10.1038/ncomms6405; b) Gu, Y.; Chang, D.-L.; Leng, X.-B.; Gu, Y.-C; Shen, Q. *Organometallics*, **2015**, *34*, 3065.

12. a) Tang, X. J.; Dolbier, Jr. W. R. *Angew. Chem. Int. Ed.* **2015**, *54*, 4246; b) Zafrani, Y.; SodMoriah, G.; Segall, Y. *Tetrahedron*, **2009**, *65*, 5278.

13. Zafrani, Y.; Sod-Moriah, G.; Segall, Y. *Tetrahedron*, **2009**, *65*, 5278.

14. CF_3SCl was reported to have an $L(ct)_{50}$ of between 440 and 880 ppm min^{-1}. Stump, E. C. *Chem. Eng. News* **1967**, *45*, 44.

15. Moore, G. G. I. *J. Org. Chem.* **1979**, *44*, 1708.

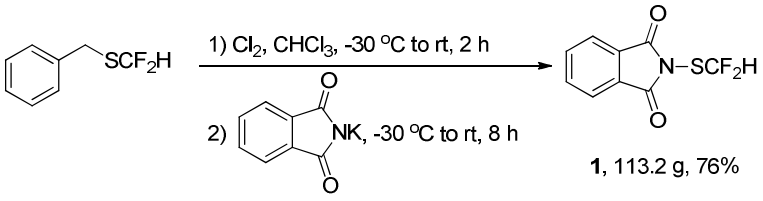
16. Okui, S.; Kyomura, N.; Fukuchi, T.; Okano, K.; He, L.; Miyauchi, A. US 7371768 B2, **2008**.

17. Honeker, R.; Ernest, B.; Glorius, F. *Chem. Eur. J.* **2015**, *21*, 8047.

18. De Leersnyder H.; Bresson J. L.; de Blois M. C.; Souberbielle J. C.; Mogenet A.; Delhotal-Landes B.; Salefranque F.; Munnich A. *J. Med. Genet.* **2003**, *40*, 74.

19. Flynn, R. M.; Burton, D. J. *J. Fluorine Chem.* **2011**, *132*, 815.

Table of Content



1, 113.2 g, 76%