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Synthesis of 1-Tri(di)fluoromethyl 1,4-Diketones Enabled by Radical Brook Rearrangement

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Dedicated to Professor Martin Oestreich on the occasion of his 50th birthday and his receipt of the WACKER Silicone Award in 2021

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Abstract: Herein, we disclose the first and simple one-pot-two-step process to the synthesis of 1-difluoromethyl 1,4-diketones, through Mn-catalyzed radical Brook rearrangement. The methodology is also amenable to the synthesis of 1-trifluoromethyl 1,4-diketones. The products are efficiently converted to fluoroalkyl substituted furans, thiophenes, pyrroles and pyridazines which are important structural motifs in natural products and pharmaceuticals.

1,4-diketones[1] are among the most useful precursors to synthesize furans, thiophenes, pyrroles and pyridazines, which are important structural motifs in natural products and pharmaceuticals such as Lophotoxin,[2] non-natural amino acid Fmoc-D-3-Ala(2-thienyl)-OH,[3] Minaprine[4] and Liptor (Figure 1).[5] In this scenario, much effort has been devoted to the synthesis of 1,4-diketones.[6] Among various 1,4-diketones, fluorinated ones are attracting chemists' more and more attention, since fluorine incorporation has become a routine strategy in drug development.[7] It is well known that the introduction of fluorine or fluoroalkyl groups can often bring beneficial effects to the parent molecules by changing the physical, chemical and biological properties. Among various fluoroalkyl groups, CF_3 is of particular importance due to its strong electron-withdrawing property and chemical stability.[8]

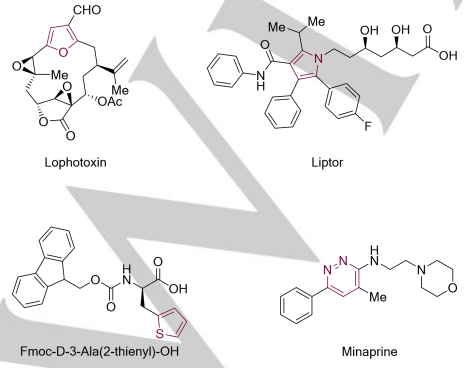
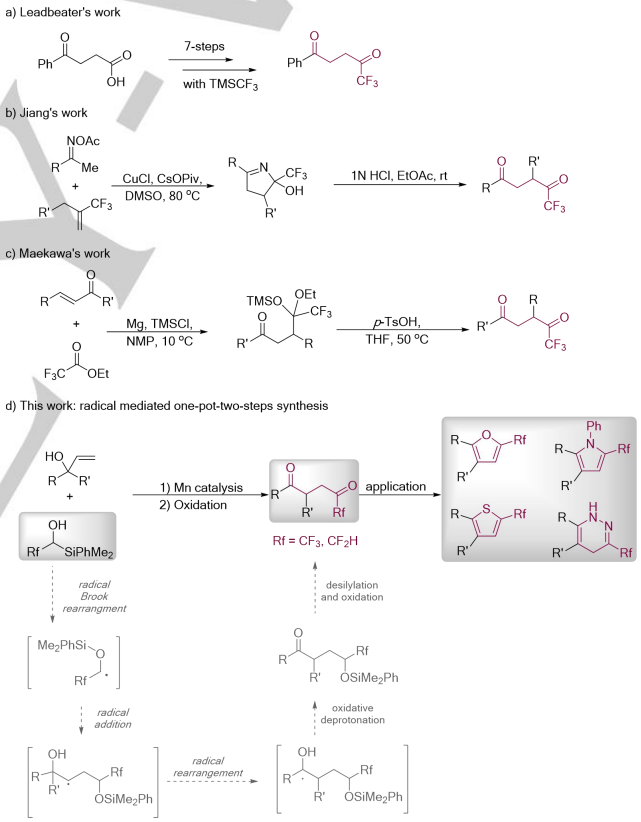


Figure 1. Representative examples of biologically active molecules with hetero-aromatic rings.



Scheme 1. Background and our strategy for the synthesis of 1-tri(di)fluoromethyl 1,4-Diketone.

CF_2H is also very valuable since it can not only mimic OH and SH groups but also behaves as a hydrogen donor through hydrogen bonding.[9] Therefore, 1-trifluoromethyl and 1-difluoromethyl 1,4-diketones are desired compounds for the synthesis of fluoroalkylated biological important furans, thiophenes, pyrroles and pyridazines.

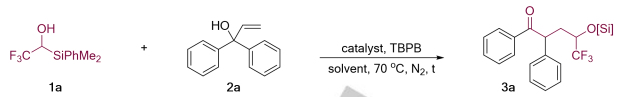
Traditional ways to prepare trifluoromethyl substituted 1,4-diketones are based on the two electron processes.[10] For example, Leadbeaters and coworkers reported the reaction with 3-benzoylpropionic acid as starting material and TMS-CF_3 as

trifluoromethyl source (Scheme 1a).[10a] Since there were two reaction sites, it was essential to protect the benzyl carbonyl group, and therefore the whole synthesis took seven steps in total, including protection, nucleophilic reaction and deprotection steps. Jiang and co-workers reported a copper-catalyzed cross-dehydrogenative coupling reaction for the synthesis of 2-(trifluoromethyl)dihydropyrrole, which could be hydrolyzed to trifluoromethylated 1,4-diketones containing R substituents next to the trifluoroacetyl group (Scheme 1b).[10b] Maekawa's group also disclosed a Mg-mediated reductive trifluoroacetylation of *α*,*β*-unsaturated ketones in the synthesis of 1-trifluoromethyl 1,4-diketones in two steps and the R substituent was next to the trifluoroacetyl group (Scheme 1c).[10c] *However, all of these studies are limited to the synthesis of 1-trifluoromethyl 1,4-diketones, and there have been no practical method for the synthesis of 1-difluoromethyl 1,4-diketones, which might because the acidic C-H bond of CF_2H group would cause problem in the synthesis via ionic reaction conditions.* To the best of our knowledge, there was only one patent mentioned the synthesis and application of 1-difluoromethyl 1,4-diketones.[11] Herein, We disclosed a simple synthesis of both 1-trifluoromethyl 1,4-diketones and 1-difluoromethyl 1,4-diketones based on an single electron reaction process, in which radical Brook rearrangement[12,13] was one of the key steps (Scheme 1d). The potential of this advance was highlighted by the synthesis of fluoroalkyl substituted heterocycles such as furans, thiophenes, pyrroles and pyridazine.

We have reported two fluorinated organosilicon reagents as trifluoroethanol and difluoroethanol transferring reagents for the synthesis of tri- and di-fluorinated alcohols that proceeds via a Mn catalyzed radical Brook rearrangement.[13a] We envisioned that the ketyl radicals generated through Brook rearrangement could add to the double bond of an allylic alcohol, and then new ketyl radical could be formed via a neophyl-type radical rearrangement, which could be further oxidized and deprotonated to generate ketone-containing silyl ether product.[14] After suitable desilylation and oxidation conditions, the final fluoroalkyl 1,4-diketone compound could be prepared (Scheme 1d).

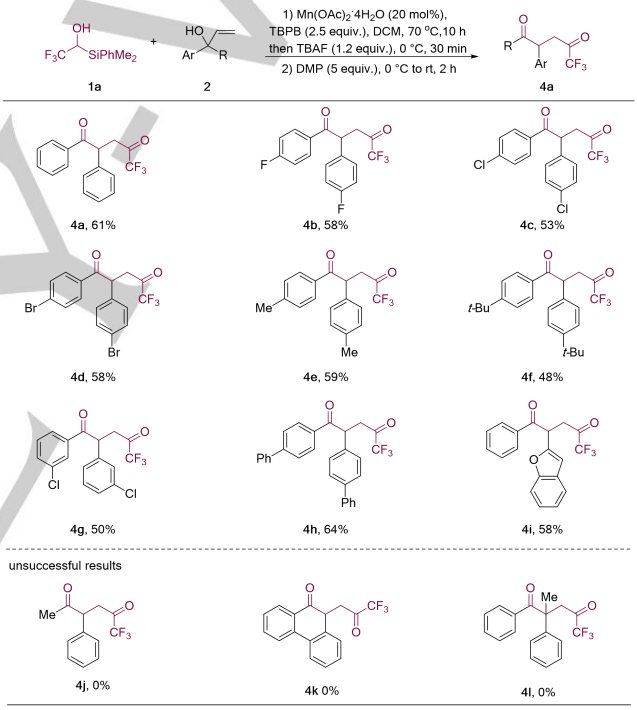
With this idea in mind, we first tested the radical reaction between *β*-fluorinated organosilicon reagent **1a** and *α*, *α*-diphenyl allylic alcohol **2a**. We used 20 mol% of $Mn(OAc)_2$•$2H_2O$ as catalyst and 2.5 equivalent of TBPB as oxidant to explore the influence of solvent on the efficiency of the reaction (Table 1, entry 1~6). It was found that DCM was the best solvent (65% yield, Table 1, entry 6), while hexane afforded similar yield (Table 1, entry 5) and MTBE, THF, dioxane and toluene afforded much lower yield (Table 1, entries 1~4). Next, we explored the ratio of reagents to get a better yield (Table 1, entries 7~9). When the amount of **1a** was increased to 3 equivalents, the yield improved to 72% (Table 1, entry 7). We got better yield when excess of **2a** was employed, and when **1a**/**2a** is 1/3, a yield of 81% was obtained for **3a** (Table 1, entry 9). Decreasing the amount of TBPB to 2 equivalent would reduce the yield (Table 1, entry 10). It was found that $Mn(OAc)_3$•$2H_2O$ can also be used as catalyst, and 78% yield of **3a** was obtained (Table 1, entry 11). The addition of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) completely inhibited the formation of product **3a** (Table 1, entry 12), supporting that the reaction might proceed through a radical mechanism.[13a]

Table 1. Optimization of reaction conditions.



entry	1a/2a/TBPB	catalyst	solvent	t/h	yield (%)[a]
1	2/1/2.5	$Mn(OAc)_2·4H_2O$ (20 mol%)	MTBE	14	trace
2	2/1/2.5	$Mn(OAc)_2·4H_2O$ (20 mol%)	THF	14	4
3	2/1/2.5	$Mn(OAc)_2·4H_2O$ (20 mol%)	Dioxane	14	20
4	2/1/2.5	$Mn(OAc)_2·4H_2O$ (20 mol%)	Toluene	14	33
5	2/1/2.5	$Mn(OAc)_2·4H_2O$ (20 mol%)	Hexane	14	64
6	2/1/2.5	$Mn(OAc)_2·4H_2O$ (20 mol%)	DCM	14	65
7	3/1/2.5	$Mn(OAc)_2·4H_2O$ (20 mol%)	DCM	14	72
8	1/2/2.5	$Mn(OAc)_2·4H_2O$ (20 mol%)	DCM	14	70
9	1/3/2.5	$Mn(OAc)_2·4H_2O$ (20 mol%)	DCM	10	81
10	1/3/2.0	$Mn(OAc)_2·4H_2O$ (20 mol%)	DCM	14	52
11	1/3/2.5	$Mn(OAc)_3·2H_2O$ (20 mol%)	DCM	14	78
12[b]	1/3/2.5	$Mn(OAc)_2·4H_2O$ (20 mol%)	DCM	10	0

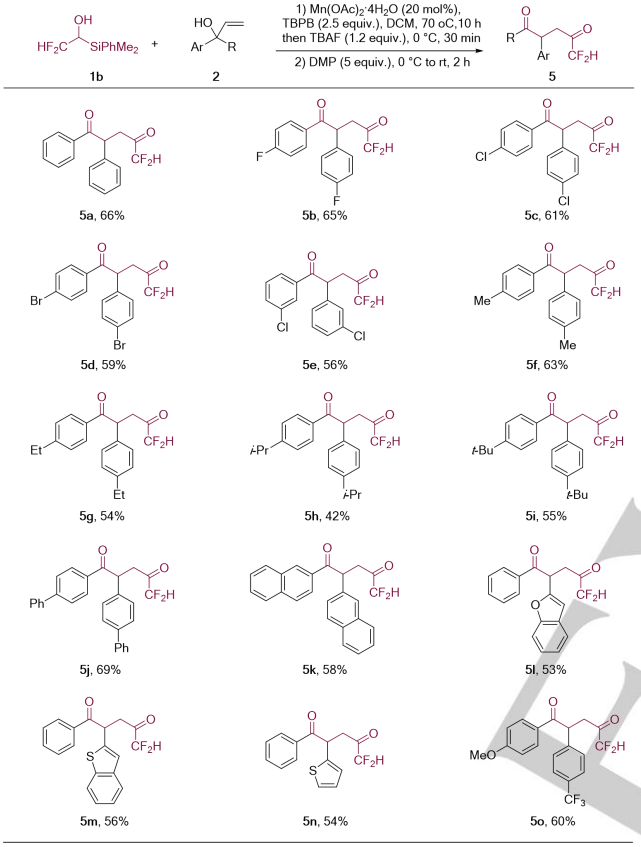
[a] The yield of the product **3a** was determined by ^{19}F NMR with $PhCF_3$ as an internal standard. [b] 3 equiv. of TEMPO was added. TEMPO: 2,2,6,6-tetramethyl-1-piperidinyloxy. TBPB: *tert*-buty peroxybenzoate.



Scheme 2. Substrate scope of the synthesis of 1-trifluoromethyl 1,4-diketones. The reactions were carried out on 0.2 mmol scale and the yield referred to isolated yield. TBAF: *tetra*-*n*-butylammonium fluoride. DMP: Dess-Martin periodinane.

Further investigation revealed that 1-trifluoromethyl 1,4-diketone **4a** could be easily obtained, when the coupling reaction between **1a** and **2a** was quenched by *tetra*-*n*-butylammonium fluoride (TBAF) followed by Dess-Martin oxidation (61% isolated yield, Scheme 2). Aryl with halogen or alkyl substitution could be used as migrating groups to obtain the target products in moderate yields (**4a**-**4g**, 48%-61% yield). In addition, the biphenyl group could also be tolerated (**4h**, 64% yield). We then found that heteroaryl had better migratory aptitude, and only the product derived of benzofuran migration was obtained (**4i**, 58% yield). This migration order is constant to the previous report,

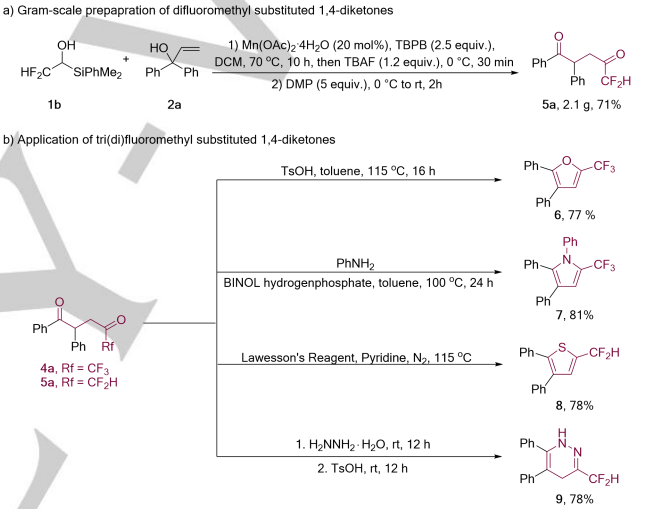
and it was proposed that the radicals might prefer to attack the heteroaryl group with lower energy level of LUMO in the intramolecular radical cyclization process.[15] Unfortunately, when we used α-alkyl-α-aryl alcohol as the substrate, we did not get the target product **4j**. 9-Vinyl-9H-fluoren-9-ol was a more challenging substrate because of the difficulty in the opening of the stable five-member ring, and no desired **4k** was obtained. There was no product **4l** formed when the methyl group was at the β-position of the alkene, which might be resulted from the steric hindrance.



Scheme 3. Substrate scope of the synthesis of 1-difluoromethyl 1,4-diketones. The reactions were carried out on 0.2 mmol scale and the yield referred to isolated yield.

Considering the importance of difluoromethyl group in pharmaceutical chemistry and the fact that there has been no general methodology reported in the synthesis of 1-difluoromethyl 1,4-diketones,[9,11] we decided to test whether our strategy could be applied in the preparation of this kind of compounds. Delightedly, the reaction between reagent **1b** and various vinyl diaryl alcohols proceeded well, affording the desired products **5a**-**5l** in 42%-69% yield (Scheme 3). The large naphthyl group could also function as a migration group to produce corresponding product **5k** in 58% yield. Alcohols which contain heteroaryl groups, such as benzofuryl, benzothienyl, and thienyl groups could also be employed as the substrates, affording the heterocyclic group migrated products **5l**, **5m** and **5n** in 53%, 56% and 54% yield, respectively. Then, the allyl alcohol with different aryl groups (**2o**) was tested, and we found that the migration of the aryl group which contain electron withdrawing CF_3 group was favored, giving product **5o** in 60% yield.

To show the general applicability of this protocol, the reaction was carried out at 10 mmol scale and we successfully prepared 2.1 grams of **5a** in 71% yield (Scheme 4a). The obtained tri(di)fluoromethyl substituted 1,4-diketones **4a** and **5a** are ideal precursors for the synthesis of fluoroalkyl substituted heterocycles (Scheme 4b). Under the catalysis of p-TsOH, compound **4a** has been converted to trifluoromethylated furan derivative **6** in 77% yield. When 1,4-diketone **4a** was treated with aniline in the presence of BINOL hydrogenphosphate in toluene at 100 °C for 24 h, trifluoromethylated pyrrole derivative **7** was obtained in 81% yield. The reaction between 1,4-diketone **5a** with Lawesson's reagent performed well in pyridine, and difluoromethylated thiophene derivative **8** has been made in 78% yield. Last but not least, the condensation reaction of **5a** with hydrazine hydrate efficiently afforded difluoromethyl containing dihydropyridazine compound **9** in 78% yield.



Scheme 4. Gram-scale reaction and the application of fluoroalkyl substituted 1,4-diketones in the synthesis of fluoroalkyl heterocycles.

In summary, we have developed a practical reaction for the synthesis of 1-trifluoromethyl and 1-difluoromethyl 1,4-diketones enabled by radical Brook rearrangement and Dess-Martin oxidation. The synthetic potential of this advance has been highlighted by the facile conversion of these products to fluoroalkylated furans, thiophenes, pyrroles and pyridazines. Because of the importance of heterocycles and fluorine incorporation in drug development, we believe our methodology will attract interests not only from synthesis field but also from medicinal and agrochemical fields. Further studies on the application of radical Brook rearrangement of organosilicon reagents in the synthesis of important organofluorine compounds are underway in our laboratory.

Acknowledgements ((optional))

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Keywords: Difluoromethyl • Fluorine • Ketones • Radical Brook rearrangement • Trifluoromethyl

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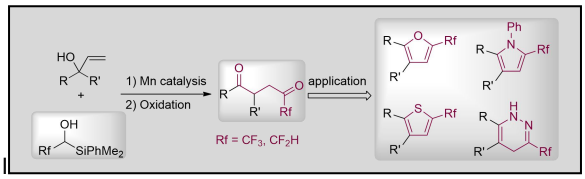

The application of Mn-catalyzed radical Brook rearrangement of fluorinated organosilicon reagents in the synthesis of 1-trifluoromethyl and 1-difluoromethyl 1,4-diktones have been disclosed for the first time. The potential of this advance have been highlighted by the transformation of the products to biologically important fluoroalkylated heterocycles.

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