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Letter

Trifluoromethylation of Benzoic Acids: An Access to Aryl Trifluoromethyl Ketones

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Cite This: *Org. Lett.* 2021, 23, 4930–4934

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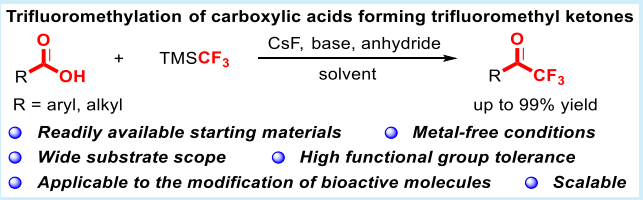
ABSTRACT: The trifluoromethylation of benzoic acids with $TMSCF_3$ was achieved through nucleophilic substitution with the use of anhydrides as an in situ activating reagent. Under the reaction conditions, a wide range of carboxylic acids including the bioactive ones worked well, thus providing a facile and efficient method for preparing aryl trifluoromethyl ketones from the readily available starting materials.



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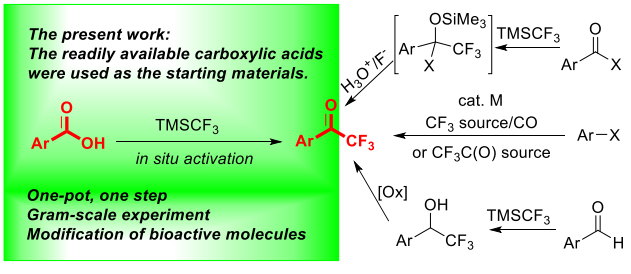
The introduction of fluorine is a strategy to enhance or change the physical and chemical performance of functional molecules in chemical science,[1] material science,[2] and biological science.[3] In particular, it is reported that ca. 20% of medicines and 30% of pesticides contain at least one fluorine atom.[4] Trifluoromethyl ketones are a kind of important organofluorine compound. In addition to the lipophilicity and metabolic stability,[5] these compounds also exhibit strong electron-withdrawing ability and are capable of forming stable hydrates.[6] These specific properties have lead to their wide application in drug design and development. Trifluoromethyl ketones are also important building blocks for other fluorine-containing functional molecules due to the diverse reactivity of the carbonyl group. Traditionally, the nucleophilic substitution of aryl metals (Li or Mg) with trifluoroacetyl derivatives can produce trifluoromethyl ketones;[7] however, the harsh reaction conditions limit the application. The Friedel−Crafts acylation of electron-rich arenes is also used despite the narrow substrate scope and issues of regioselectivity.[8] Thus the development of more efficient methods for their preparation is of current concern (Scheme 1).[9] Nowadays, the transition-metal-catalyzed trifluoroacetylation of aryl halides/pseudohalides has been developed for preparing these compounds.[10] The oxidation of α-trifluoromethyl alcohols is also extensively used;[11] however, the alcohols should be presynthesized from the unstable aldehydes; overstoichiometric special oxidants are also required.

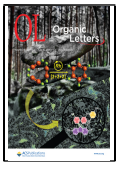
Herein we report a trifluoromethylation of benzoic acids with $TMSCF_3$ to produce aryl trifluoromethyl ketones in good to high yields (Scheme 1). Carboxylic acids are abundant and readily available raw chemicals. Compared with the aromatic aldehydes and aryl halides used in the established reactions, they are cheaper and environmentally benign. To our knowledge, the synthesis of trifluoromethyl ketones through the direct trifluoromethylation of carboxylic acids has never been achieved. It should be noted that carboxylic derivatives such as acyl halides,[12] esters,[13] and Weinreb amides[14] can also produce trifluoromethyl ketones through the addition with $TMSCF_3$ and the subsequent H_3O^+/F^- treatment (Scheme 1). The multistep operation, that is, the presynthesis of starting materials and the two-step reaction process, reduces the step efficiency and atomic utilization.

A mixture of 4-phenyl benzoic acid and $TMSCF_3$ (3 equiv) dissolved in PhOMe was allowed to react at 120 °C for 15 h in the presence of TFAA (2 equiv) and DMAP (2.5 equiv), and the corresponding aryl trifluoromethyl ketone (**3a**) was produced in 80% yield (Table 1, entry 1). By adding 2.5 equiv of CsF to the reaction mixture, the yield of **3a** was increased to 90% (Table 1, entry 2). Lowering the reaction temperature to 100 °C led to a slight decrease in the yield, whereas the reaction efficiency was also not enhanced when the reaction was conducted at 140 °C (Table 1, entries 3 and 4). The choice of an in situ activating reagent was essential to

Scheme 1. Synthesis of Aryl Trifluoromethyl Ketones



Received: May 22, 2021
Published: June 10, 2021



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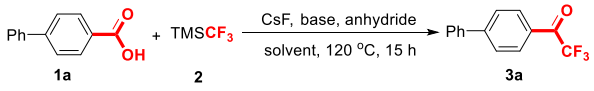
https://doi.org/10.1021/acs.orglett.1c01720
Org. Lett. 2021, 23, 4930–4934

Table 1. Trifluoromethylation of 4-Phenyl Benzoic Acid with $TMSCF_3$[a]



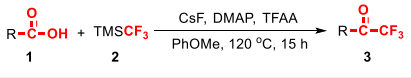
entry	anhydride	base	solvent	yield (%)[b]
1[c]	TFAA	DMAP	PhOMe	80
2	TFAA	DMAP	PhOMe	90
3[d]	TFAA	DMAP	PhOMe	57
4[e]	TFAA	DMAP	PhOMe	80
5		DMAP	PhOMe	N.D.
6	Piv_2O	DMAP	PhOMe	N.D.
7	Ac_2O	DMAP	PhOMe	N.D.
8	Boc_2O	DMAP	PhOMe	N.D.
9	Ms_2O	DMAP	PhOMe	19
10	Tf_2O	DMAP	PhOMe	41
11	TFAA		PhOMe	N.D.
12	TFAA	$NaHCO_3$	PhOMe	N.D.
13	TFAA	Na_2CO_3	PhOMe	trace
14	TFAA	Et_3N	PhOMe	trace
15	TFAA	DBU	PhOMe	trace
16	TFAA	pyridine	PhOMe	trace
17	TFAA	DMAP	THF	60
18	TFAA	DMAP	cyclohexane	71
19	TFAA	DMAP	NMP	28
20	TFAA	DMAP	CH_3CN	77
21	TFAA	DMAP	toluene	64
22	TFAA	DMAP	1,4-dioxane	72

[a]Reaction conditions: 4-phenyl benzoic acid **1a** (0.2 mmol), $TMSCF_3$ (**2**, 3.0 equiv), anhydride (2.0 equiv), CsF (2.5 equiv), base (2.5 equiv), solvent (2.0 mL), N_2, 120 °C, 15 h. TFAA, trifluoroacetic anhydride; DMAP, 4-dimethylaminopyridine. DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene. NMP, *N*-methyl pyrrolidone. [b]GC yields using dodecane as an internal standard. [c]Without CsF. [d]140 °C. [e]100 °C.

this reaction. No product was detected without anhydride or with Piv_2O, Ac_2O, or Boc_2O (Table 1, entries 5−8). Low yields were also given when Ms_2O and Tf_2O were used instead (Table 1, entries 9 and 10). The base was also an important factor for this reaction. No reaction took place in its absence (Table 1, entry 11). No or only a trace amount of **3a** was obtained with the use of $NaHCO_3$, Na_2CO_3, Et_3N, DBU, or pyridine under similar reaction conditions (Table 1, entries 12−16). Finally, this reaction could also occur in other selected solvents such as THF, cyclohexane, NMP, CH_3CN, toluene, and 1,4-dioxane, but the yields decreased to some extent (Table 1, entries 17−22).

With the optimal reaction conditions in hand, we subsequently investigated the substrate scope of this trifluoromethylation reaction. As compiled in Table 2, various carboxylic acids worked well under the present reaction conditions to produce the corresponding trifluoromethyl ketones in good to high yields. Thus in addition to **1a**, a high yield was obtained from 3-phenyl benzoic acid (Table 2, entry 2). Probably because of the steric hindrance, the yield slightly decreased with 2-phenyl benzoic acid (Table 2, entry 3). Other substrates with electron-donating groups such as cyclohexyl, *tert*-butyl, and methoxy groups, the easily hydrolytic phenoxy groups, and the alkaline dimethylamino groups were also smoothly transformed into the expected products in high yields (Table 2, entry 4−8). Halo iodine survived well in

Table 2. Trifluoromethylation of Carboxylic Acids with $TMSCF_3$[a]



Entry	Acids **1**	$TMSCF_3$ **2**	Product **3**, GC (isolated) yield
1	**1a**, R = 4-Ph		**3a**, R = 4-Ph, 90 (86)%
2	**1b**, R = 3-Ph		**3b**, R = 3-Ph, 85 (87)%
3	**1c**, R = 2-Ph		**3c**, R = 2-Ph, 77 (68)%
4	**1d**, R = 4-*n*-hexyl		**3d**, R = 4-*n*-hexyl, 82 (79)%
5[b]	**1e**, R = 4-*t*-Bu		**3e**, R = 4-*t*-Bu, 88 (80)%
6	**1f**, R = 4-OMe		**3f**, R = 4-OMe, 76 (76)%
7	**1g**, R = 4-OPh		**3g**, R = 4-OPh, 78 (74)%
8	**1h**, R = 4-NMe_2		**3h**, R = 4-NMe_2, 71 (68)%
9[bc]	**1i**, R = 4-I		**3i**, R = 4-I, 96 (89)%
10[bc]	**1j**, R = 2-I		**3j**, R = 2-I, 79 (72)%
11[c]	**1k**, R = 4-NO_2		**3k**, R = 4-NO_2, 85 (75)%
12[c]	**1l**, R = 4-CN		**3l**, R = 4-CN, 84 (81)%
13	**1m**, R = 4-PhC(O)		**3m**, R = 4-PhC(O), 73 (72)%
14	**1n**, R^1 = 2-Me, R^2 = 4-OMe		**3n**, R^1 = 2-Me, R^2 = 4-OMe, 73 (71)%
15[b]	**1o**, R^1 = 3-Cl, R^2 = 5-OMe		**3o**, R^1 = 3-Cl, R^2 = 5-OMe, 99 (99)%
16[b]	**1p**		**3p**, 71 (63)%
17	**1q**		**3q**, 76 (70)%
18	**1r**		**3r**, 67 (64)%
19	**1s**, R = H		**3s**, R = H, 79 (73)%
20	**1t**, R = 6-OMe		**3t**, R = 6-OMe, 70 (71)%
21	**1u**, R = 6-Br		**3u**, R = 6-Br, 86 (84)%
22	**1v**		**3v**, 85 (78)%
23[d]	**1w**		**3w**, 81 (70)%
24[e]	**1x**		**3x**, 97%
25[b]	**1y**		**3y**, Z = O, 72 (64)%
26	**1z**		**3z**, Z = S, 77 (68)%
27[f]	**1aa**		**3aa**, 46(44)%
28[f]	**1ab**		**3ab**, 44(43)%

[a]Reaction conditions: acid **1** (0.2 mmol), $TMSCF_3$ (**2**, 3.0 equiv), TFAA (2.0 equiv), CsF (2.5 equiv), DMAP (2.5 equiv), PhOMe (2.0 mL), N_2, 120 °C, 15 h. GC yields using dodecane as an internal standard. The data in parentheses are the isolated yields. [b]GC yield using tridecane as an internal standard. [c]80 °C. [d]Product is a mixture of **3w** and its hydration **3w′**. (See the SI.) [e]^{19}F NMR yield using 4-fluorobenzoic acid as an internal standard. [f]$TMSCF_3$ (**2**, 1.0 equiv), TFAA (1.5 equiv), 100 °C.

the current reaction system, facilitating the further functionalization of the products via cross-coupling (Table 2, entries 9

https://doi.org/10.1021/acs.orglett.1c01720
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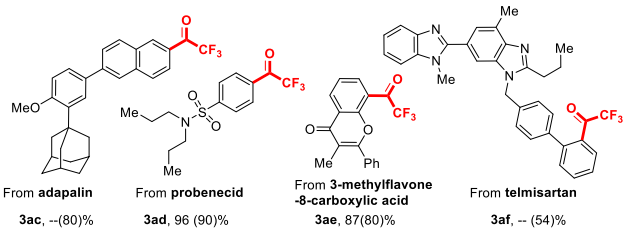
and 10). The electron-deficient substrates were also applicable to this reaction. For example, benzoic acids bearing electron-withdrawing groups such as NO_2, CN, and PhC(O) worked well, producing the trifluoromethylating products in high yields (Table 2, entries 11−13). Under the present reaction conditions, the di- and trisubstituted benzoic acids proved to be the right substrate (Table 2, entries 14−17). It is worth noting that piperic acid and trimethylgallic acid are important medicinal intermediates, and they were readily trifluoromethylated by the strategy (Table 2, entries 16 and 17). Good to high yields of trifluoromethyl ketones were obtained from the polycyclic and heterocyclic aromatic carboxylic acids (Table 2, entries 18−26). Aliphatic carboxylic acids, exemplified as stearic acid and oleic acid, were also applicable to this reaction, although relatively low yields were given (Table 2, entries 27 and 28).[15] The low yields might be ascribed to the relatively high electron density of the carbonyl carbon, which is not beneficial for the nucleophilic addition.

Interestingly, this reaction was applicable to the direct modification of bioactive carboxylic acids, generating the corresponding trifluoromethyl ketones (Scheme 2). For

Scheme 2. Modification of Bioactive Molecules[a]

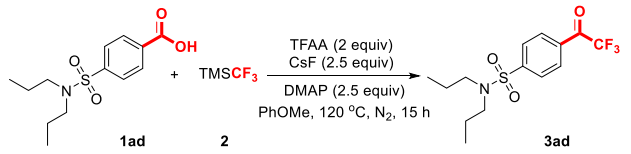


[a]Reaction conditions: acid **1** (0.2 mmol), $TMSCF_3$ (**2**, 3.0 equiv), TFAA (2.0 equiv), CsF (2.5 equiv), DMAP (2.5 equiv), PhOMe (2.0 mL), N_2, 120 °C, 15 h. GC yields using dodecane as an internal standard. The data in parentheses are the isolated yields.

example, adapalin, a clinical drug for skin disease, was readily trifluoromethylated to produce **3ac** in 80% yield. Probenecid is used as an antigout drug and an antibiotic adjuvant. It also worked well to give the target product **3ad** in 90% yield under the reaction conditions. 3-Methylflavone-8-carboxylic acid is a clinical drug for the treatment of coronary heart disease. It was also transformed into the expected product **3ae** in 80% yield. By this strategy, telmisartan, a kind of antihypertensive drug, was also proved to be the right substrate (**3af**).

Practically, this reaction was scalable. As shown in Scheme 3, we chose the drug probenecid as the model substrate and carried out three trifluoromethylation reactions on a 1, 2, and 5 mmol scale. After work up and isolation through a SiO_2 chromatographic column, high yields were obtained for all

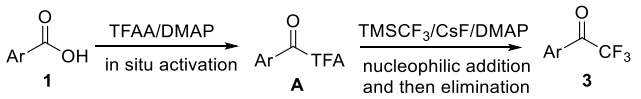
Scheme 3. Gram-Scale Experiments



three reactions. The results well demonstrated the practicality of this new reaction in organic synthesis.

On the basis of previous literature,[12−14,16] a plausible mechanism for this trifluoromethylation reaction is proposed in Scheme 4. Initially, the carboxylic acid **1** was activated in

Scheme 4. Proposed Mechanism



situ by TFAA to produce a mixing anhydride **A**.[16] By the aid of CsF and DMAP, the resulting mixing anhydride **A** underwent nucleophilic addition with $TMSCF_3$[12−14] and then elimination to give the corresponding product **3**.

In summary, we have disclosed an efficient synthesis of the value-added trifluoromethyl ketones from the environmental benign and readily available carboxylic acids. The reaction conditions were facile and relatively mild. A wide substrate scope and high functional group tolerance were demonstrated. The bioactive functional molecules such as adapalin, probenecid, 3-methylflavone-8-carboxylic acid, and telmisartan were also smoothly trifluoromethylated to produce the corresponding products. In addition, this reaction is scalable. These results showed the potential synthetic value of this new reaction in organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01720.

General information, experimental procedures, characterized data, and copies of ^1H and ^{13}C NMR and ^{19}F NMR spectroscopies (PDF)

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https://doi.org/10.1021/acs.orglett.1c01720
Org. Lett. 2021, 23, 4930−4934

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Partial financial support from the Key R&D project of Hainan province (no. ZDYF2020168) and National Natural Science Foundation of China (no. 21871070) is gratefully acknowledged. We also thank Miss Mengjie Cen for reproducing **3f** and **3y** by the strategy.

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https://doi.org/10.1021/acs.orglett.1c01720
Org. Lett. 2021, 23, 4930−4934