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# A Powerful Cascade Approach for Expeditious Synthesis of Trifluoromethylated Furans

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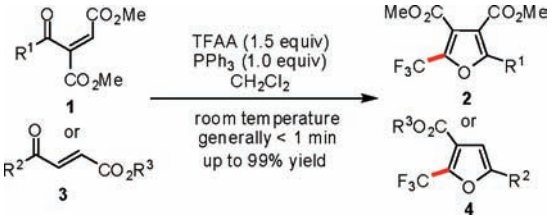
## ABSTRACT




**A powerful approach to synthesize trifluoromethylated furans has been developed. The method is operationally simple, broad in substrate scope, and amenable to scale-up using trifluoroacetic anhydride. Meanwhile, the strategy not only provided a versatile approach to synthesize trifluoromethylated furans but also provides a new method for exploring the new reactivity of trifluoroacetic anhydride.**

Trifluoromethylated compounds have found broad applications in medicinal,[1] agrochemical,[2] and material science.[3] Trifluoromethyl-substituted furan derivatives, with thousands of them patented as drug molecules, are a highly valuable class of heterocyclic compounds with remarkable biological activities. More specifically, a large number of reported pharmacologically active compounds have been shown to contain a subunit of either type A or B (Figure 1),[4] and these bioactive compounds have been used for treatment of various diseases[4] such as cancers,[4g,f] HIV,[4b] obesity,[4j] diabetes,[4j,n] gastrointestinal[4i]/sleep[4e] disorders, neurodegenerative[4c]/hyperproliferative[4d]/ autoimmune[4h] diseases, inflammations,[4m] and numerous others. Needless to say, this kind of compound has been proven to be an excellent drug candidate and hence has generated great interest in the pharmaceutical sector (for example,

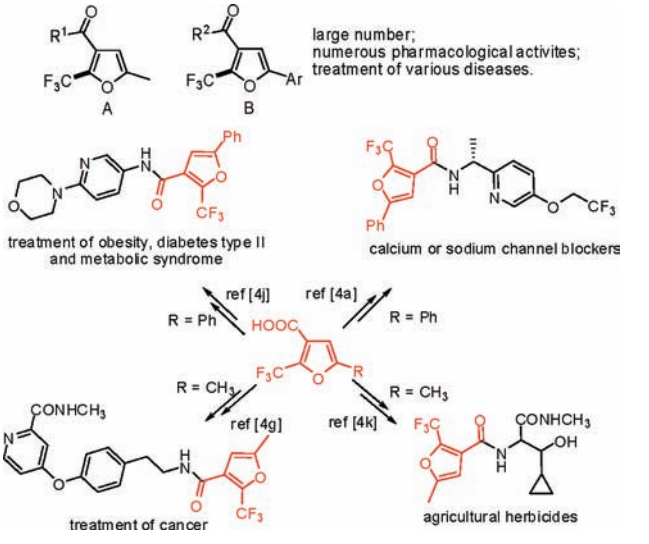



**Figure 1.** Examples of biologically active furan derivatives.

Roche,[4e,j] Merck,[4d] Takeda,[4f,n] Abbott,[4h] Astrazeneca,[4i] Basf,[4k] Bayer,[4l] Aventis,[4m] etc.). Even though such compounds are

(1) (a) Purser, S.; More, P. R.; Swallow, S.; Gouverneuer, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (b) Filler, R.; Kobayashi, Y.; Yagupolski, L. M. *Organofluorine Compounds in Medicinal Chemistry & Biomedical Applications*; Elsevier: Amsterdam, 1993.

(2) (a) Banks, R. E.; Smart, B. E.; Tatlow, C. J. *Organofluorine Chemistry, Principles and Comercial Applications*; Springer: New York, 1994. (b) Jeschke, P. *ChemBioChem* **2004**, *5*, 570.

(3) (a) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Wiley-VCH: Weinheim, 2004. (b) Yamamoto, H.; Hiyama, T.; Kanie, K.; Kusumoto, T.; Morizawa, Y.; Shimzu, M. *Organofluorine Compounds: Chemistry and Application*; Springer: Berlin, 2000.

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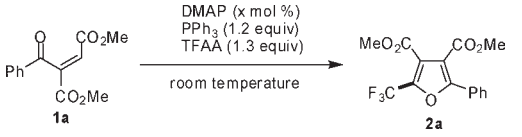
present in some agricultural products,[4k,l] it is not practical to obtain them in large amounts for downstream usage. Consequently, the exploitation of simple methods for the synthesis of this kind of compound and its derivatives are becoming extremely important.

However, despite the pharmaceutical importance of trifluoromethylated furans, only very few methods have been reported for the synthesis of this kind of compound due to the difficulty in constructing these molecules,[5] and these limited methods heavily involved the use of transition metals and required energy-consuming high temperatures. Furthermore, the synthesis of functionalized trifluoromethylated furans mainly requires multiple steps and specially tailored building blocks. Thus, these synthesis methods, to the best of our knowledge, still suffer from several disadvantages, such as high temperatures, very low product yields, time-consuming multiple synthesis steps, and use of toxic transition metals and special reagents.[5] Notably, a much more practical problem is that almost all of these reported approaches have been limited in substrate selection.[6] Particularly, time and energy economy are important aspects of streamlining a synthesis route since our whole society makes every effort to save energy and reduce emission.

Clearly, a mild, straightforward, and broadly applicable method for the formation of trifluoromethylated furans is highly desired. There are several significant issues that must be addressed to develop a useful method for this purpose. These issues include the following: (1) the exploration of time and energy economy for the process; (2) the development of efficient and step-economical[7] methods with high yields, preferably metal-free cascade approaches; (3) the use of low-cost, reliable, and simple $CF_3$ sources; (4) the development of a facile method with a broad substrate scope which can be easily adapted to scale-up; (5) the addition of one more functional group onto the furan ring to provide novel opportunities for drug design and discovery. Herein, we report our preliminary findings toward solving these challenging problems.

**Table 1.** Optimization of Reaction Conditions[a]




| entry | solvent | $x$ mol (%) | time | yield (%)[b] |
|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | 10 | <1 min | 95 |
| 2 | $CH_2Cl_2$ | 5 | <1 min | 91 |
| 3 | $CH_2Cl_2$ | 1 | <1 min | 93 |
| 4 | $CH_2Cl_2$ | 0 | <1 min | 95 |
| 5 | toluene | 0 | <1 min | 89 |
| 6 | $CH_3CN$ | 0 | <1 min | 91 |
| 7[c] | $CH_2Cl_2$ | 0 | <1 min | 94 |
| 8[d] | $CH_2Cl_2$ | 0 | <1 min | 93 |
| 9[e] | $CH_2Cl_2$ | 0 | <1 min | 99 |

[a] Unless otherwise noted, the reactions were performed with **1a** (0.20 mmol), TFAA (0.26 mmol), $PPh_3$ (0.24 mmol), and DMAP ($x$ mol %) in solvent (1.0 mL) at room temperature within 1 min. [b] Yield of isolated product. [c] 1.5 equiv of $PPh_3$ was used. [d] 1.0 equiv of $PPh_3$ was used. [e] 1.0 equiv of $PPh_3$ and 1.5 equiv of TFAA were used. equiv = equivalent, TFAA = trifluoroacetic anhydride, DMAP = 4-dimethylaminopyridine.

Initially, we considered a practical question of whether or not the direct and synthetically efficient transfer of a $CF_3$ group from trifluoroacetic anhydride (TFAA), one of the most common reagents, would be possible, since TFAA were previously employed in the construction of special building blocks and yet had not been used directly in the process of synthesis of trifluoromethylated aromatic compounds. Then we examined the reaction of easily available compound **1a**[8] with TFAA in the presence of $PPh_3$ and a catalytic amount of DMAP in $CH_2Cl_2$ at room temperature (Table 1, entry 1). To our delight, the reaction

(4) Selected examples from the extensive recent patent literature: (a) Inoue, T.; Watanabe, S.; Yamagishi, T.; Arano, Y.; Morita, M.; Shimada, K. WO 2010137351, 2010. (b) Yoakim, C.; Bailey, M. D.; Bilodeau, F.; Carson, R. J.; Fader, L.; Kawai, S.; Laplante, S.; Simoneau, B.; Surprenant, S.; Thibeault, C.; Tsantrizos, Y. S. WO 2010130034, 2010. (c) Griffioen, G.; Van Dooren, T.; Rojas de la Parra, V.; Marchand, A.; Allasia, S.; Kilonda, A.; Chaltin, P. WO 2010142801, 2010. (d) Sutton, A. E.; Richardson, T. E.; Huck, B. R.; Karra, S. R.; Chen, X.; Xiao, Y. ; Goutopoulos, A.; Lan, R.; Perrey, D.; Vandeveer, H. G.; Liu-Bujalski, L.; Stieber, F.; Hodous, B. L.; Qiu, H.; Jones, R. C.; Heasley, B. WO 2010093419, 2010. (e) Knust, H.; Nettekoven, M.; Pinard, E.; Roche, O.; Rogers-Evans, M. US 20090163485, 2009. (f) Sakai, N.; Imamura, S.; Miyamoto, N.; Hirayama, T. WO 2008016192, 2008. (g) Gould, A. E.; Greenspan, P. D.; Vos, T. J. WO 2008030448, 2008. (h) George, D. M.; Dixon, R. W.; Friedman, M.; Hobson, A.; Li, B.; Wang, L.; Wu, X.; Wishart, N. WO 2008060621, 2008; (i) Bauer, U.; Brailsford, W.; Gustafsson, L; Svensson, T. WO 2007073300, 2007. (j) Bolin, D. R.; Cheung, A. W.-H.; Firooznia, F.; Hamilton, M. M.; Li, S.; McDermott, L. A.; Qian, Y.; Yun, W. WO 2007060140, 2007. (k) Witschel, M.; Zagar, C.; Hupe, E.; Kuehn, T.; Moberg, W. K.; Parra Rapado, L.; Stelzer, F.; Vescovi, A.; Rack, M.; Reinhard, R.; Sievernich, B.; Grossmann, K.; Ehrhardt, T. WO 2006125687, 2006. (l) Mansfield, D.; Rieck, H.; Coqueron, P.-Y.; Desbordes, P.; Villier, A.; Grosjean-Cournoyer, M.-C.; Genix, P. WO 2006108791, 2006. (m) Borcherding, D. R.; Gross, A.; Shum, P. W.-K.; Willard, N.; Freed, B. S. WO 2004100946, 2004. (n) Hamamura, K.; Sasaki, S.; Amano, Y.; Sakamoto, J.; Fukatsu, K. WO 2004022551, 2004.

(5) For an excellent review: (a) Petrov, V. A. *Fluorinated Heterocyclic Compounds: Synthesis, Chemistry, and Applications*; Wiley: Hoboken, NJ, 2009 and references cited therein; for selected examples: (b) Kino, T.; Nagase, Y.; Ohtsuka, Y.; Yamamoto, K.; Uraguchi, D.; Tokuhisa, K.; Yamakawa, T. *J. Fluorine Chem.* **2010**, *131*, 98. (c) Pang, W.; Zhu, S.; Xin, Y.; Jiang, H.; Zhu, S. *Tetrahedron* **2010**, *66*, 1261. (d) Zhang, D.; Yuan, C. *Eur. J. Org. Chem.* **2007**, 3916. (e) Bouillon, J.-P.; Kikelj, V.; Tinant, B.; Harakat, D.; Portella, C. *Synthesis* **2006**, 1050. (f) Aristov, S. A.; Vasil'ev, A. V.; Rudenko, A. P. *Russ. J. Org. Chem.* **2006**, *42*, 66. (g) Bouillon, J.-P.; Hénin, B.; Huot, J.-F.; Portella, C. *Eur. J. Org. Chem.* **2002**, 1556. (h) Linderman, R. J.; Jamois, E. A.; Tennyson, S. D. *J. Org. Chem.* **1994**, *59*, 957. (i) Begue, J.-P.; Bonnet-Delpon, D.; Dogbeavou, R.; Ourevitch, M. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2787. (j) Bucci, R.; Laguzzi, G.; Pompili, M. L.; Speranzia, M. *J. Am. Chem. Soc.* **1991**, *113*, 4544. (k) Sawada, H.; Nakayama, M. *J. Fluorine Chem.* **1990**, *46*, 423. (l) Neumann, D.; Kischkewitz, J. *J. Fluorine Chem.* **1990**, *46*, 265. (m) Jullien, J.; Pechine, J. M.; Perez, F.; Piade, J. J. *Tetrahedron* **1982**, *38*, 1413. (n) Bambury, R. E.; Yaktin, H. K.; Wyckoff, K. K. *J. Heterocycl. Chem.* **1968**, *5*, 95.

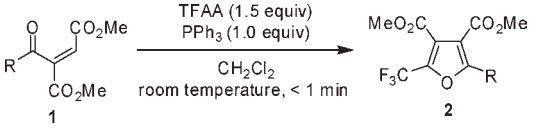
(6) To the best of our knowledge, there are only two methods reported thus far that investigated more than five different substrates (see ref 5c and 5d) and many cases only employed one or two substrates (see ref 5).

(7) (a) Wender, P. A.; Miller, B. L. *Nature* **2009**, *460*, 197. (b) Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40.

(8) (a) Nair, V.; Sreekanth, A. R.; Abhilash, N.; Biju, A. T.; Devi, B. R.; Menon, R. S.; Rath, N. P.; Srinivasc, R. *Synthesis* **2003**, 1895. (b) Li, C.-Q.; Shi, M. *Org. Lett.* **2003**, *5*, 4273.

proceeded efficiently and afforded the desired product in 95% yield. Most remarkably, the reaction occurred immediately and was completed in seconds. We next reduced the catalyst loading to 5 and 1 mol %, respectively, and the reactions proceeded similarly (Table 1, entries 2 and 3). The following study revealed that catalyst DMAP was not necessary for this reaction (Table 1, entry 4). Solvent screening showed that $CH_2Cl_2$ was an optimal selection (Table 1, entries 4–6). Further tests by adjusting the amount of $PPh_3$ and TFAA disclosed that the best result was obtained (99% yield) by using 1.0 equiv of $PPh_3$ and 1.5 equiv of TFAA (Table 1, entry 9). The structure of the product was clearly established by single crystal X-ray diffraction of **2h**.[9]

**Table 2.** Substrate Scope[a]

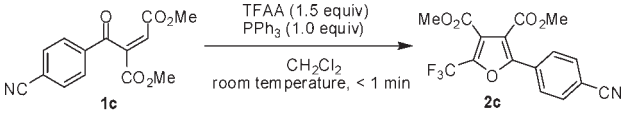



| entry | 1 | R | products | yield (%)[b] |
|---|---|---|---|---|
| 1 | **1a** | Ph | **2a** | 99 |
| 2 | **1b** | 3-$NO_2C_6H_4$ | **2b** | 97 |
| 3 | **1c** | 4-$CNC_6H_4$ | **2c** | 99 |
| 4 | **1d** | 4-$CF_3C_6H_4$ | **2d** | 97 |
| 5 | **1e** | 2-$ClC_6H_4$ | **2e** | 93 |
| 6 | **1f** | 3-$ClC_6H_4$ | **2f** | 99 |
| 7 | **1g** | 4-$FC_6H_4$ | **2g** | 99 |
| 8 | **1h** | 4-$BrC_6H_4$ | **2h** | 99 |
| 9[c] | **1i** | 2-$OMeC_6H_4$ | **2i** | 92 |
| 10[c] | **1j** | 2-$MeC_6H_4$ | **2j** | 91 |
| 11 | **1k** | 4-$CH_3C_6H_4$ | **2k** | 87 |
| 12 | **1l** | 4-$OMeC_6H_4$ | **2l** | 97 |
| 13 | **1m** | 2-furyl$C_6H_4$ | **2m** | 95 |

[a] Unless otherwise noted, all the reactions were performed with **1** (0.2 mmol), TFAA (0.3 mmol), and $PPh_3$ (0.2 mmol) in $CH_2Cl_2$ (1.0 mL) at room temperature. [b] Yield of isolated product. [c] The reaction was allowed to proceed for 5 min.

Under the optimal reaction conditions, the scope of the cascade reaction was then investigated by using a variety of substrates to establish the generality of the process (Table 2). The cascade process was found to be broad in scope, with very good to excellent yields obtained for all products (**2**; 87–99%). The reaction allowed incorporation of a wide range of functional groups in the furan products. The aromatic groups bearing electron-withdrawing or -donating groups were both well tolerated, as were ortho-, meta-, and para-substituted aromatic rings. Sterically demanding substrates (Table 2, entries 9 and 10) and heteroaromatic groups, such as furan (Table 2, entry 13), were also successfully converted into the corresponding products with excellent yields. More importantly, this cascade protocol is also amenable to scale-up. When the reaction was carried out on a 5 mmol (**1c**, 1.375 g) scale, it also was completed in seconds and afforded the product in 96% yield. We then further conducted the reaction on a 40 mmol (**1c**, 10.920 g) scale and found the reaction was as efficient as the smaller scale reaction, completing in seconds with the same excellent yield (scheme 1). Therefore, this method is fast, easy to handle, and adaptable to large-scale synthesis.

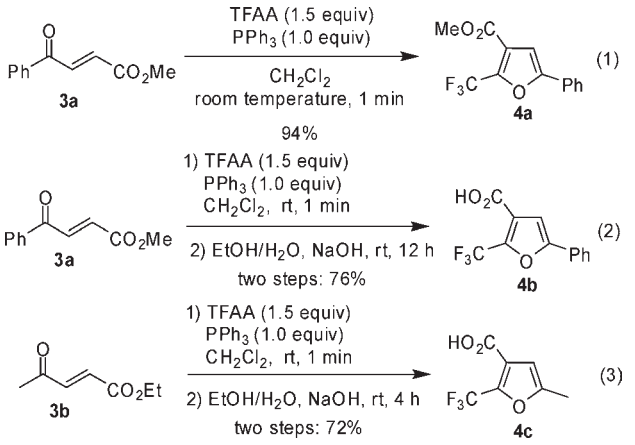
**Scheme 1.** Example of Scalable Synthesis




**1c**: 5 mmol, 1.365 g; **2c**: 1.699 g, 96% yield.
**1c**: 40 mmol, 10.920 g; **2c**: 13.565 g, 96% yield.

We next focused on the synthesis of biologically attractive furan derivatives of type A and B. Under the optimized reaction conditions, the cascade process was efficient for either type A or B synthesis. Both aromatic and alkyl substrates could be successfully employed in this cascade process (Scheme 2). The expected product **4a** was obtained with excellent yield (94%) by the use of substrate **3a**. A one-pot cascade formation of furan and ester hydrolysis were also successful in affording the desired products with good yield (**4b**, 76%; **4c**, 72%). Since furans **4b**, **4c** and their derivatives[4] are known intermediates extensively used in the synthesis of a large number of drug molecules[4] (for example, see figure 1), it is of crucial importance for them to be efficiently synthesized.

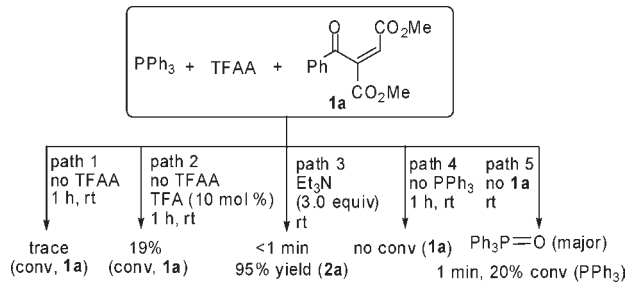
**Scheme 2.** Synthesis of A- and B-Type Compounds




A series of control experiments were carried out to determine the triggering step (see Supporting Information for details). The reactions were performed in the absence of TFAA, $PPh_3$, and **1a,** respectively (Scheme 3). Omission of TFAA only gave a trace amount of conversion with respect

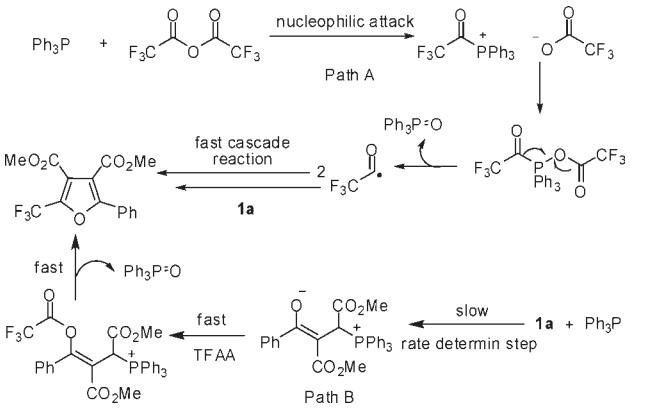
(9) CCDC 830674 (**2h**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

**Scheme 3.** Control Experiments




to **1a** even when the reaction was conducted for 1 h (path 1). Then we questioned whether or not the trace amount of TFA decomposed from TFAA in the reaction system triggered the reaction in the initial step as a Brønsted acid catalyst. In fact, when we added 10 mol % TFA to the reaction mixture of $PPh_3$ and **1a**, an improved conversion of 19% compared to path 1 was observed (path 2). However, the major products of the two paths were different as detected by $^1H$ NMR analysis (see Supporting Information). To further justify the role of TFA, TFAA was added to an alkaline reaction mixture of 3.0 equiv of $Et_3N$, $PPh_3$, and **1a** (path 3). The reaction was as efficient as in the previous study (Table 1), and this observation indicates that a Brønsted acid catalyst is not needed for the success of this cascade reaction. As expected, omission of $PPh_3$ afforded no conversion of **1a** even after 1 h (path 4). In the absence of **1a**, the reaction was conducted for 1 min and gave 20% conversion of $PPh_3$ to a new product (path 5). Further analysis showed that triphenylphosphine oxide, which is associated with new $CF_3$-containing fragments or compounds generated during the reaction as observed by $^{19}F$ NMR analysis (see Supporting Information for details), was formed as a major product in this reaction. During a prolonged reaction time, a much more complex mixture of trifluoromethylated/fluorinated fragments/compounds was detected by $^{19}F$ NMR analysis. Taking all the evidence together, it is likely that TFAA and $PPh_3$ reacted rapidly to generate a highly reactive intermediate that triggered and participated in this complicated transformation reaction (Scheme 4, path A). However, the reaction pathway in which $PPh_3$ and **1a** reacted slowly initially and then TFAA participated and promoted the following steps for expeditious synthesis of trifluoromethylated furan is still a possible approach (Scheme 4, path B).

**Scheme 4.** Possible Reaction Pathways




In summary, we have developed a time and energy economical method for the synthesis of drug-related trifluoromethylated furans. This cascade approach is extremely efficient since the reaction was completed just in seconds and afforded the desired products with very good to excellent yields. Furthermore, this method is operationally simple with wide substrate generality and amenable to scale-up. Notably, the simple and commonly available $CF_3$ source TFAA was employed in trifluoromethylated heterocyclic compound synthesis.

Therefore, this strategy provides a new general approach for activation and application of TFAA. We expect this novel method to be of broad utility in the synthesis of biologically active medicinal agents. We are continuing to explore the mechanism of this reaction with various anhydrides and study the bioactivities of these furan derivatives. The results of these investigations will be reported elsewhere.

**Acknowledgment.** We are grateful for the NSFC (21032005, 20972058), the National Basic Research Program of China (Nos. 2009CB626604, 2010CB833203),the "111" program from MOE of P. R. China, the Fundamental Research Funds for the Central Universities (lzujbky-2009-159), and a Syngenta fellowship to Y. Wang.

**Supporting Information Available.** Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.