GDCh

Trifluoromethylation

Synthesis of α-Trifluoromethylated Ketones from Vinyl Triflates in the Absence of External Trifluoromethyl Sources

Takuji Kawamoto,* Rio Sasaki, and Akio Kamimura*

Abstract: A novel method for the conversion of vinyl triflates into a-trifluoromethylated ketones in the absence of external trifluoromethyl sources is described. This process accomplishes an efficient migration of the trifluoromethyl group of the triflate to the a-position in the ketone through a radical process. The reaction proceeds by the addition of a trifluoromethyl radical to the vinyl triflate and subsequent fragmentation of the trifluoromethane sulfonyl radical. Based on this reaction, a one-pot two-step procedure for the trifluoromethylation of ketones was developed. The method presented herein also allows the transfer of perfluoroalkyl groups from vinyl perfluoroalkanesulfonates, which are readily accessible from alkynes and perfluoroalkanesulfonic acids.

Trifluoromethylation is an important transformation as the introduction of a trifluoromethyl group endows pharmaceuticals, agrochemicals, and building blocks in materials science with a variety of interesting properties.^[1] Over the past decade, considerable effort has been dedicated to the efficient introduction of trifluoromethyl groups.^[2] Key compounds for the preparation of such fluorinated products are α-trifluoromethylated ketones, which have been widely employed. For the preparation of such trifluoromethylated ketones, several methods have been developed. For example, the use of the Umemoto reagent and the Togni reagent efficiently achieves the electrophilic trifluoromethylation of enolates (Scheme 1 a).^[3] The nucleophilic trifluoromethylation of α -haloketones with CuCF₃ has recently been reported by Grushin et al. (Scheme 1b),^[4] while the radical trifluoromethylation of enolates is well established (Scheme 1c). In 1990, Oshima, Utimoto, and co-workers reported the first radical trifluoromethylation of silyl or germyl enol ethers initiated by triethylborane (BEt₃),^[5] and the scope of this radical trifluoromethylation was subsequently extended by Mikami and coworkers, who used other initiators.^[6] Recently, MacMillan et al. reported that such trifluoromethylations can be initiated by irradiation with visible light.^[7] Since all these methods require external trifluoromethyl sources, which often contain large activating groups and/or heavy metals, this situation can still be improved.

 [*] Dr. T. Kawamoto, R. Sasaki, Prof. Dr. A. Kamimura Department of Applied Chemistry, Yamaguchi University Ube, Yamaguchi 755-8611 (Japan)
 E-mail: tak102@yamaguchi-u.ac.jp ak10@yamaguchi-u.ac.jp

Supporting information and the ORCID identification number(s) for
 the author(s) of this article can be found under http://dx.doi.org/10.
 1002/anie.201608591.





Vinyl triflates are valuable electrophiles for a variety of transition-metal-catalyzed coupling reactions.^[8] In comparison, their use in radical reactions has received less attention.^[9,10] In 2010, for example, Kim and co-workers reported that vinyl triflates react with activated alkyl halides to form α alkylated ketones (Scheme 2a). This procedure could also be applied to the alkylation to unactivated C-H bonds (Scheme 2b). It should be noted that the trifluoromethyl radical plays an important role in the reaction, even though it is consumed during the process. Incorporating vinyltriflatederived trifluoromethyl radicals into the final products would open a new avenue in trifluoromethylation chemistry. Herein, we report the BEt₃-initiated radical trifluoromethylation of vinyl triflates (Scheme 2c). We developed a one-pot protocol that enables the trifluoromethylation of ketones without the isolation of pregenerated vinyl triflates. Furthermore, we



Scheme 2. Radical reactions of vinyl triflates. EWG = electron-withdrawing group.

Angew. Chem. Int. Ed. 2016, 55, 1-5

© 2016 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

These are not the final page numbers!

Wiley Online Library

examined the potential use of vinyl perfluoroalkanesulfonates for the synthesis of perfluoroalkylation products.

For our initial study, we chose 1-(4-chlorophenyl)vinyl trifluoromethanesulfonate (1a) as a model substrate (Table 1). Treatment of 1a in toluene with $BEt_3^{[11]}$ (0.5 equiv) as a radical initiator afforded 1-(4-chlorophenyl)-3,3,3-trifluoropropan-1-one (2a) in 15% yield (entry 1). A GC-MS analysis indicated that methylbenzotrifluoride was formed as a side product. This side reaction could be suppressed by the use of benzotrifluoride (BTF) instead of toluene, and it also increased the yield of 2a to 60% (entry 2). A further screening of solvents revealed that CH₂ClCH₂Cl afforded 2a in even better yield (entries 3–7). The use of azobisisobutyronitrile (AIBN) instead of BEt₃ was not effective.

Table 1: Optimization of the reaction conditions.[a]

	CI	t, RT, 14 h	CF3
1a		2a	
Entry	Solvent	Conv. [%] ^[b]	Yield [%] ^[b,c]
1	PhCH₃	33	15
2	PhCF ₃ (BTF)	97	60
3	CH₃CN	100	71
4	THF	73	29
5	<i>c</i> -C ₆ H ₁₂	93	58
6	CH_2Cl_2	99	71
7	CH ₂ ClCH ₂ Cl	97	83 (64)

[a] **1a** (0.3 mmol, 0.33 M), BEt₃ (1 M in hexanes, 0.15 mL, 0.5 equiv). [b] Determined by ¹H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard. [c] Yield of product, isolated after flash column chromatography on SiO₂, is given within parentheses. THF = tetrahydrofuran.

Encouraged by these results (Table 1), we then examined the generality of the trifluoromethylation using a variety of vinyl triflates (Table 2). The reaction of 1-phenylvinyl trifluoromethanesulfonate (1b) furnished the trifluoromethylated 2b in 76% yield (entry 2). p-Halo- and p-estersubstituted vinyl triflates (1c-f) afforded 2c-f in good yields (entries 3-6). The reaction of the cyclic enolate 1g also worked well, thus yielding ketone 2g in 58% yield (entry 7). Conversely, the reaction of o- and m-substituted vinyl triflates 1h,i furnished 2h,i in merely moderate yields under these reaction conditions, while the starting materials could be recovered (entries 8 and 10). In these cases, the addition of 2,6-di-tert-butylpyridine improved the yield of 2h and 2i to 74 and 52%, respectively (entries 9 and 11). The triflate 1j did not generate the desired product 2j (entry 12). Thus, the reaction is chemoselective toward aryl-substituted vinyl triflates. This chemoselectivity is nicely illustrated by the treatment of a mixture of 1f and 1j with BEt₃, a reaction which resulted in the selective formation of 2 f in 74% yield (Scheme 3).

Moreover, we examined a one-pot synthesis for α -trifluoromethylated ketones (Scheme 4). For example, the treatment of 4-chloroacetophenone (**1a**') with trifluorome-

 Table 2:
 Radical trifluoromethylation of vinyl triflates.^[a]



[a] **1** (0.3 mmol, 0.33 M), BEt₃ (1 M in hexanes, 0.15 mL, 0.5 equiv), CH₂ClCH₂Cl (1 mL). [b] Determined by ¹H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard. [c] Yield of product, isolated from flash column chromatography on SiO₂, is given within parentheses. [d] 2,6-di-*tert*-butylpyridine (1.2–1.3 equiv) was added.



Scheme 3. Chemoselective transformation of aryl-substituted vinyl triflates.

thanesulfonic anhydride (Tf₂O) and 2,6-di-*tert*-butylpyridine (DTBP) resulted in the formation of the vinyl triflate 1a.^[12] Then, BEt₃ (0.5 equiv) was added to the reaction mixture, and furnished 2a in 79% yield. This one-pot procedure offers substantial advantages, especially for the trifluoromethylation

www.angewandte.org

© 2016 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 4. One-pot synthesis of α -trifluoromethylated ketones.

of labile vinyl triflates derived from either 4-acetylbiphenyl $(1\mathbf{k}')$ or 2-acetonaphtone $(1\mathbf{l}')$, which readily undergo hydrolysis during column chromatography on SiO₂. Using this onepot protocol afforded the trifluoromethylated $2\mathbf{k}$ and $2\mathbf{l}$ in 59 and 37 % yield, respectively, upon isolation.

A plausible mechanism for this reaction is shown in Scheme 5. Although the mechanism of the initiation step,^[13,14] that is, the formation of the trifluoromethyl radical is not entirely clear at this stage, these radicals could react with the vinyl triflate to afford the radical **A**, which could then undergo β -fission to generate the α -trifluoromethylated ketone **2** and trifluoromethanesulfonyl radical **B**, from which the trifluoromethyl radical could be regenerated rapidly upon extrusion of SO₂.^[15]



Scheme 5. Proposed mechanism for the radical-mediated synthesis of α -trifluoromethylated ketones.

Finally, we show that this method can also be used for the synthesis of α -perfluoroalkylated ketones (Scheme 6). Under the aforementioned optimized reaction conditions, **2m** and **2n** were generated in 59 and 53% yield, respectively, upon isolation. These results clearly suggest that the present method is quite effective for the preparation of various types of α -perfluoroalkyl ketones.



Angewandte

Chemie

Scheme 6. Synthesis of α -perfluoroalkylated ketones **2m** and **2n** from vinyl perfluoroalkanesulfonates **1m** and **1n**.

In conclusion, we report the first example of a straightforward method for the preparation of α -trifluoromethylated ketones from vinyl triflates in the absence of external trifluoromethyl sources. Therein, the vinyl triflates act simultaneously as the trifluoromethyl radical source and as the radical acceptor. We have also developed a simple and efficient one-pot synthesis for the formation of α -trifluoromethylated ketones from ketones. The results of this study should contribute substantially to the advancement of trifluoromethylation chemistry.

Experimental Section

The following trifluoromethylation of a vinyl triflates can be considered representative: a solution of 1-(4-chlorophenyl)vinyl trifluoromethanesulfonate (**1a**; 95.7 mg, 0.33 mmol) in 1,2-dichloroethane (1.0 mL) was treated with BEt₃ (1.0 M in hexanes, 0.16 mL). The reaction mixture was stirred for 14 h at room temperature before water (3 mL) was added, and the resulting mixture was extracted with dichloromethane (3×5 mL). The combined extracts were concentrated in vacuo, and the residue was purified by flash column chromatography (silica gel, hexane-EtOAc, 15:1, v/v) to afford **2a** in 64% yield (47.6 mg, 0.21 mmol).

The following procedure is representative for the one-pot fluoroalkylation of acetophenone derivatives: a solution of 4chloroacetophenone (**1**a'; 76.7 mg, 0.50 mmol) in 1,2-dichloroethane (2.0 mL) was treated with Tf₂O (0.13 mL, 0.75 mmol, 1.5 equiv) and 2,6-di-*tert*-butylpyridine (198 mg, 1.0 mmol, 2.0 equiv). After 2 h, BEt₃ (1.0 m in hexanes, 0.25 mL) was added and the reaction mixture was stirred for 14 h at room temperature before water (3 mL) was added, and the resulting mixture was extracted with dichloromethane (3 × 10 mL). The combined extracts were concentrated in vacuo, and the residue was purified by flash column chromatography (silica gel, hexane-EtOAc, 15:1, v/v) to afford **2a** in 63% yield (69.6 mg, 0.31 mmol).

Acknowledgments

This work was partially supported by the Asahi Glass Foundation and a JSPS Grant-in-Aid for Young Scientists (B) (16K17869).

Keywords: boranes · radicals · reaction mechanisms · synthetic methods · trifluoromethylation

www.angewandte.org

These are not the final page numbers!



- a) K. Müller, C. Faeh, F. Diederich, *Science* 2007, *317*, 1881;
 b) W. K. Hagmann, *J. Med. Chem.* 2008, *51*, 4359;
 c) N. A. Meanwell, *J. Med. Chem.* 2011, *54*, 2529;
 d) Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev.* 2016, *116*, 422.
- [2] For selected reviews on trifluoromethylation reactions, see:
 a) A. Studer, Angew. Chem. Int. Ed. 2012, 51, 8950; Angew. Chem. 2012, 124, 9082; b) H. Egami, M. Sodeoka, Angew. Chem. Int. Ed. 2014, 53, 8294; Angew. Chem. 2014, 126, 8434; c) J. Charpentier, N. Früh, A. Togni, Chem. Rev. 2015, 115, 650; d) E. Merino, C. Nevado, Chem. Soc. Rev. 2014, 43, 6598; e) L. Chu, F.-L. Qing, Acc. Chem. Res. 2014, 47, 1513; f) J. Xu, X. Liu, Y. Fu, Tetrahedron Lett. 2014, 55, 585; g) C. Zhang, Adv. Synth. Catal. 2014, 356, 2895; h) X. Liu, C. Xu, M. Wang, Q. Liu, Chem. Rev. 2015, 115, 683.
- [3] For selected examples on electrophilic trifluoromethylation reactions, see: a) T. Umemoto, S. Ishihara, J. Am. Chem. Soc. 1993, 115, 2156; b) T. Umemoto, K. Adachi, J. Org. Chem. 1994, 59, 5692; c) A. Togni, Chimia 2008, 62, 261; for a recent review on electrophilic trifluoromethylation, see: d) A. Prieto, O. Baudoin, D. Bouyssi, N. Monteiro, Chem. Commun. 2016, 52, 869.
- [4] a) P. Novák, A. Lishchynskyi, V. V. Grushin, J. Am. Chem. Soc. 2012, 134, 16167; b) Z. Mazloomi, A. Bansode, P. Benavente, A. Lishchynskyi, A. Urakawa, V. V. Grushin, Org. Process Res. Dev. 2014, 18, 1020.
- [5] a) K. Miura, M. Taniguchi, K. Nozaki, K. Oshima, K. Utimoto, *Tetrahedron Lett.* **1990**, *31*, 6391; b) K. Miura, Y. Takeyama, K. Oshima, K. Utimoto, *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1542.
- [6] a) Y. Itoh, K. Mikami, Org. Lett. 2005, 7, 649; b) Y. Itoh, K. Mikami, J. Fluorine Chem. 2006, 127, 539; c) Y. Itoh, K. Mikami, Org. Lett. 2005, 7, 4883; d) Y. Itoh, K. Mikami, Tetrahedron 2006, 62, 7199; e) K. Mikami, Y. Tomita, Y. Ichikawa, K. Amikura, Y. Itoh, Org. Lett. 2006, 8, 4671; f) Y. Itoh, K. N. Houk, K. Mikami,

J. Org. Chem. **2006**, *71*, 8918; g) Y. Tomita, Y. Ichikawa, Y. Itoh, K. Kawada, K. Mikami, *Tetrahedron Lett.* **2007**, *48*, 8922.

- [7] P. V. Pham, D. A. Nagib, D. W. C. MacMillan, Angew. Chem. Int. Ed. 2011, 50, 6119; Angew. Chem. 2011, 123, 6243.
- [8] For selected examples on cross-coupling reactions using vinyl triflates as electrophiles, see: a) V. Saini, M. O'Dair, M. S. Sigman, J. Am. Chem. Soc. 2015, 137, 608; b) R. Tomita, T. Koike, M. Akita, Angew. Chem. Int. Ed. 2015, 54, 12923; Angew. Chem. 2015, 127, 13115.
- [9] J. Lee, K.-C. Lim, X. Meng, S. Kim, Synlett 2010, 1647.
- [10] Oshima and Utimoto reported one example of a trifluoromethylation of vinyl triflates using CF_3I as the trifluoromethyl radical source. See Ref. [5a].
- [11] a) P. Renaud in *Encyclopedia of Radicals in Chemistry, Biology* and Materials, Vol. 2 (Eds.: C. Chatgilialoglu, A. Studer), Wiley, Hoboken, **2012**, pp. 601–628; b) C. Ollivier, P. Renaud, *Chem. Rev.* **2001**, *101*, 3415.
- [12] P. J. Stang, W. Treptow, Synthesis 1980, 283.
- [13] It is feasible to assume that the ethyl radical could add to the olefinic moiety to furnish an initial trifluoromethyl radical. However, we found no evidence for the generation of the corresponding ethyl-substituted acetophenones (propyl aryl ketones).
- [14] While Crich et al. reported that the homolytic substitution should not occur for sulfones, they did not mention sulfonates. See: D. Crich, T. K. Hutton, K. Ranganathan, *J. Org. Chem.* **2005**, *70*, 7672. Nevertheless, considering that the α -ethylsulfonylated ketone 1-(4-chlorophenyl)-2-(ethylsulfonyl)ethan-1-one was formed in 11 % yield (Table 1, entry 7), we cannot exclude at this point that an ethyl radical may add to the sulfonyl group of the triflate to afford a trifluoromethyl radical.
- [15] W. Dolbier, Top. Curr. Chem. 1997, 192, 97.

Received: September 2, 2016 Published online:

www.angewandte.org

C 2016 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Angew. Chem. Int. Ed. 2016, 55, 1-5



Communications

OSO₂CF₃

BEt₃



Communications

Trifluoromethylation

T. Kawamoto,* R. Sasaki, A. Kamimura* _____

Synthesis of α -Trifluoromethylated Ketones from Vinyl Triflates in the Absence of External Trifluoromethyl Sources

Sure BEt₃: A BEt₃-induced conversion of vinyl triflates into α -trifluoromethylated ketones is reported. The reaction proceeds by the addition of a trifluoromethyl radical to the vinyl triflate and subsequent

fragmentation of a trifluoromethane sulfonyl radical. This reaction was used to develop an efficient one-pot two-step procedure for the trifluoromethylation of ketones.

0

