

Cu-Mediated trifluoromethylation of benzyl, allyl and propargyl methanesulfonates with TMSCF_3

Xueliang Jiang¹ and Feng-Ling Qing^{*1,2}

Full Research Paper

Open Access

Address:

¹Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, China and ²College of Chemistry, Chemical Engineering and Biotechnology, Donghua University, 2999 North Renmin Lu, Shanghai 201620, China

Email:

Feng-Ling Qing* - flq@mail.sioc.ac.cn

* Corresponding author

Keywords:

copper; methanesulfonates; organo-fluorine; trifluoromethylation

Beilstein J. Org. Chem. **2013**, *9*, 2862–2865.

doi:10.3762/bjoc.9.322

Received: 18 September 2013

Accepted: 25 October 2013

Published: 12 December 2013

This article is part of the Thematic Series "Organo-fluorine chemistry III".

Guest Editor: D. O'Hagan

© 2013 Jiang and Qing; licensee Beilstein-Institut.

License and terms: see end of document.

Abstract

A Cu-mediated trifluoromethylation of benzyl, allyl and propargyl methanesulfonates with TMSCF_3 was developed for the first time. This method offers a convenient and economical approach to various trifluoroethyl-containing compounds.

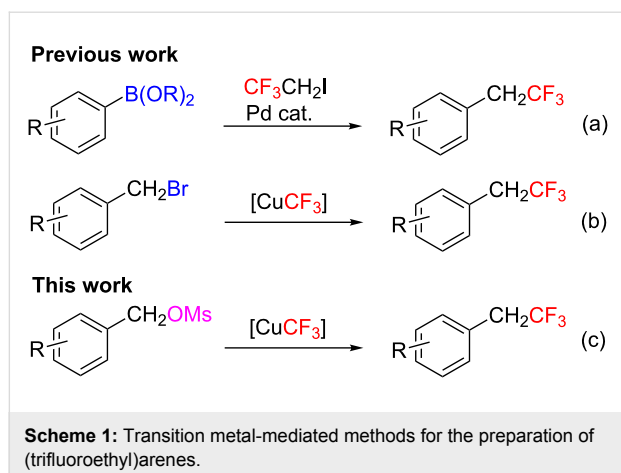
Introduction

Fluorinated organic molecules are extremely important in agrochemicals, pharmaceuticals and materials [1-6]. In recent years, (trifluoroethyl)arenes have drawn increasing attention in medicinal chemistry and related fields [7-9]. Different methods have been developed for the synthesis of (trifluoroethyl)arenes, such as Cl-F exchange of the trichloroethyl derivatives [10], reduction of the (trifluoroethyl)aryl derivatives [11] and addition of 2,2-difluorostyrene derivatives [12]. Compared to these methods, the direct transition metal-mediated trifluoroethylation of arylboronic acids [13,14] (Scheme 1a) and trifluoromethylation of benzyl halides [15-21] (Scheme 1b) are more convenient. Especially trifluoromethylations of benzyl bromides with a $[\text{CuCF}_3]$ species, which are generated from different precursors, are generally employed to afford various

(trifluoroethyl)arenes. Although these methods are proven efficient, it is still highly desirable to develop new protocols from economic consideration. In continuation of our research on transition metal-mediated trifluoromethylation [22-27], we report here the first example of Cu-mediated trifluoromethylation of benzyl methanesulfonates (Scheme 1c).

Results and Discussion

We initiated our investigation by reacting benzyl methanesulfonate **1a** with TMSCF_3 (2.0 equiv) in the presence of KF (2.0 equiv) and CuI (0.2 equiv) in DMF (2.0 mL) at 60 °C under Ar atmosphere. However, only 17% yield of the desired product **2a** was observed in this case (Table 1, entry 1). The yield was improved to 31% when the reaction was carried out in



the presence of 1,10-phenanthroline (phen) (Table 1, entry 2). Increasing the substrate concentration (from 0.1 M to 0.4 M) could further improve the product yield to 49% (Table 1, entries 3 and 4). Other copper salts such as CuBr, CuCl, CuTc and CuOAc, were next screened, but none of them was better than CuI (Table 1, entries 5–8). Interestingly, when the benzyl methanesulfonate reacted with [CuCF₃] generated in situ from TMSCF₃ and a stoichiometric amount of CuI (1.1 equiv) without phen, the desired product **2a** was formed in 68% yield (Table 1, entry 9). Decreasing or increasing the amount of CuI resulted in a lower yield (Table 1, entries 10 and 11). The solvent was next screened and, to our delight, the highest yield

of the product was achieved when using DMF/HMPA (1:1) as the mixed solvent (Table 1, entry 14).

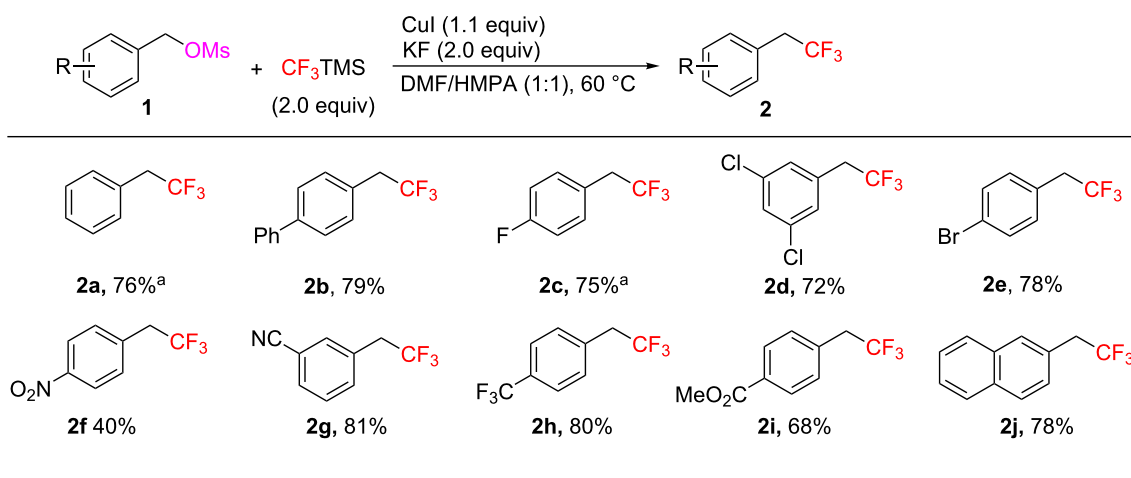
With the optimal conditions in hand, we next examined the substrate scope of the Cu-mediated trifluoromethylation of benzyl methanesulfonates with TMSCF₃ (Scheme 2). This method tolerates various functional groups. A wide range of benzyl methanesulfonates bearing electron-withdrawing groups, such as nitro (**1f**), cyano (**1g**), trifluoromethyl (**1h**) and ester (**1i**), as well as electron-donating groups such as phenyl (**1b**), smoothly underwent the transformation, affording the desired products in moderate to good yield. Importantly, both chloro (**1d**) and bromo (**1e**) substituents are also compatible with this method. It is particularly noteworthy that the reaction can be scaled up efficiently. **2a** and **2c** were successfully prepared on 10 mmol scale, indicating the good reliability of the process.

The present reaction could also be expanded to the trifluoromethylation of allylic methanesulfonates (Scheme 3). Treatment of the substrate **1k** under the standard reaction conditions afforded the linear trifluoromethylated product **2k** in 78% yield with a trace amount of Z isomer. Interesting, the reactions with the allylic methanesulfonates **1l** and **1m** gave the same regioselectivity and stereoselectivity with good yields. These observations indicate that a π-allyl/Cu^{III} complex might be involved in the C_{sp3}-CF₃ bond formation, but the detailed mechanism remains to be elucidated.

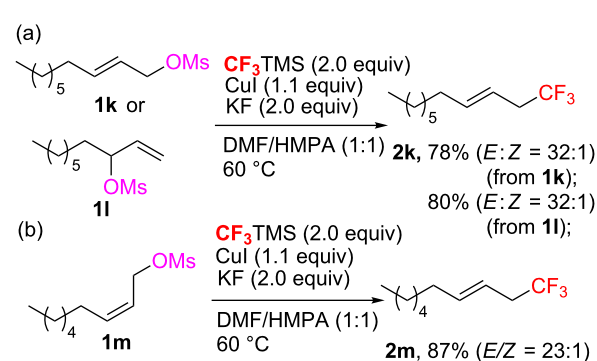
Table 1: Optimization of the reaction conditions.^a

entry	CuX (equiv)	ligand	solvent	yield of 2a (%) ^b
1 ^c	CuI (0.2)	–	DMF	17
2 ^c	CuI (0.2)	phen	DMF	31
3 ^d	CuI (0.2)	phen	DMF	32
4	CuI (0.2)	phen	DMF	49
5	CuBr (0.2)	phen	DMF	40
6	CuCl (0.2)	phen	DMF	trace
7 ^e	CuTc (0.2)	phen	DMF	trace
8	CuOAc	phen	DMF	trace
9	CuI (1.1)	–	DMF	68
10	CuI (1.5)	–	DMF	66
11	CuI (1.0)	–	DMF	62
12	CuI (1.1)	–	DMSO	38
13	CuI (1.1)	–	HMPA	9
14	CuI (1.1)	–	DMF/HMPA (1:1)	76

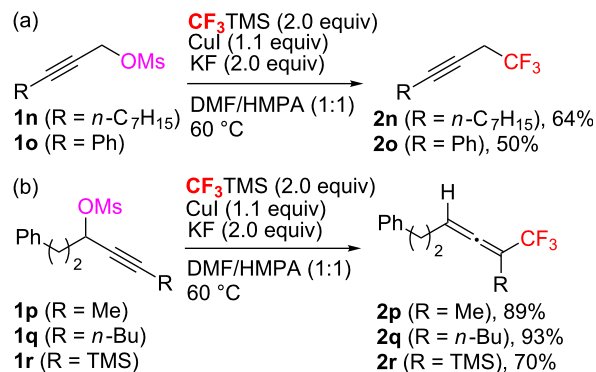
^aReaction conditions: **1a** (0.2 mmol), ligand (0.2 mmol), TMSCF₃ (0.4 mmol), KF (0.4 mmol), DMF (0.5 mL), 60 °C, under Ar atmosphere. ^bYield was determined by ¹⁹F NMR using benzo-trifluoride as an internal standard. ^c2.0 mL of DMF. ^d1.0 mL of DMF. ^eCuTc is copper(I) thiophene-2-carboxylate.



Scheme 2: Cu-mediated trifluoromethylation of benzyl methanesulfonates. Reaction conditions: **1** (2.0 mmol), CuI (2.2 mmol), TMSCF_3 (4.0 mmol), KF (4.0 mmol), DMF/HMPA (1:1, 5.0 mL), $60\text{ }^\circ\text{C}$, under Ar atmosphere; Isolated yield. ^aIsolated yield after distillation on 10.0 mmol scale.



Scheme 3: Cu-Mediated trifluoromethylation of allyl methanesulfonates.



Scheme 4: Cu-Mediated trifluoromethylation of propargyl methanesulfonates.

We were next interested in the trifluoromethylation of propargyl methanesulfonate derivatives. Both aliphatic and aryl-substituted linear propargyl methanesulfonates under standard reaction conditions afforded the corresponding trifluoromethylated propargylic products in moderate yields (Scheme 4a). However, the reaction of the branched substrates under identical conditions gave the trifluoromethylated allenyl products in good to excellent yields, without any trifluoromethylated propargylic products (Scheme 4b). Thus, this reaction provides an efficient protocol for the synthesis of allenyl- CF_3 derivatives, which are useful building blocks for pharmaceuticals [28,29].

Conclusion

In summary, we have developed an efficient copper-mediated trifluoromethylation of benzyl methanesulfonates at the benzylic position under mild conditions. The reaction can be

easily scaled up and allows for the efficient synthesis of a series of (trifluoroethyl)arenes with excellent functional group compatibility. Furthermore, the method could also be extended to the trifluoromethylation of allyl and propargyl methanesulfonates, affording the corresponding allylic-, propargylic- and allenyl- CF_3 derivatives.

Experimental

General procedure for the Cu-mediated trifluoromethylation of benzyl methanesulfonates: CuI (2.2 mmol) and KF (4.0 mmol) were added into a Schlenk tube equipped with a magnetic stirring bar under Ar atmosphere. DMF (5.0 mL) and Me_3SiCF_3 (2.0 equiv) were added. After stirring for 20 minutes, the mixture was heated to $60\text{ }^\circ\text{C}$ and then benzyl methanesulfonate (2.0 mmol) was added under N_2 atmosphere. The reaction mixture was kept at $60\text{ }^\circ\text{C}$ for 4 hours and then cooled to

room temperature. The resulting mixture was diluted with diethyl ether, washed with water and brine, dried over sodium sulfate, and concentrated. The crude products were purified by column chromatography on silica gel to give the products.

Supporting Information

Supporting Information File 1

Experimental details, characterization data of all products and copies of NMR spectra.

[<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-322-S1.pdf>]

Acknowledgements

We gratefully acknowledge National Natural Science Foundation of China (21072028, 21272036) and National Basic Research Program of China (2012CB21600).

References

- Kirsch, P. *Modern Fluoroorganic Chemistry*; Wiley-VCH: Weinheim, 2004. doi:10.1002/352760393X
- Uneyama, K. *Organofluorine Chemistry*; Blackwell: Oxford, U.K., 2006. doi:10.1002/9780470988589
- Ojima, I. *Fluorine in Medicinal Chemistry and Chemical Biology*; Wiley-Blackwell: Chichester, U.K., 2009.
- Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881–1886. doi:10.1126/science.1131943
- Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305–321. doi:10.1021/op700134j
- O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308–319. doi:10.1039/b711844a
- Shi, G. Q.; Dropinski, J. F.; Zhang, Y.; Santini, C.; Sahoo, S. P.; Berger, J. P.; MacNaul, K. L.; Zhou, G.; Agrawal, A.; Alvaro, R.; Cai, T.-Q.; Hernandez, M.; Wright, S. D.; Moller, D. E.; Heck, J. V.; Meinke, P. T. *J. Med. Chem.* **2005**, *48*, 5589–5599. doi:10.1021/jm050373g
- Parrish, C. A.; Adams, N. D.; Auger, K. R.; Burgess, J. L.; Carson, J. D.; Chaudhari, A. M.; Copeland, R. A.; Diamond, M. A.; Donatelli, C. A.; Duffy, K. J.; Faucette, L. F.; Finer, J. T.; Huffman, W. F.; Hugger, E. D.; Jackson, J. R.; Knight, S. D.; Luo, L.; Moore, M. L.; Newlander, K. A.; Ridgers, L. H.; Sakowicz, R.; Shaw, A. N.; Sung, C.-M. M.; Sutton, D.; Wood, K. W.; Zhang, S.-Y.; Zimmerman, M. N.; Dhanak, D. *J. Med. Chem.* **2007**, *50*, 4939–4952. doi:10.1021/jm070435y
- MacSari, I.; Besidski, Y.; Csajnyik, G.; Nilsson, L. I.; Sandberg, L.; Yngve, U.; Ahlin, K.; Bueters, T.; Eriksson, A. B.; Lund, P.-E.; Venyike, E.; Oerther, S.; Hygge Blakeman, K.; Luo, L.; Arvidsson, P. I. *J. Med. Chem.* **2012**, *55*, 6866–6880. doi:10.1021/jm300623u
- Ando, A.; Miki, T.; Kumadaki, I. *J. Org. Chem.* **1988**, *53*, 3637–3639. doi:10.1021/jo00250a049
- Uneyama, K.; Momota, M.; Hayashida, K.; Itoh, T. *J. Org. Chem.* **1990**, *55*, 5364–5368. doi:10.1021/jo00306a013
- Nguyen, B. V.; Burton, D. J. *J. Org. Chem.* **1997**, *62*, 7758–7764. doi:10.1021/jo971019w
- Zhao, Y.; Hu, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 1033–1036. doi:10.1002/anie.201106742
- Liang, A.; Li, X.; Liu, D.; Li, J.; Zou, D.; Wu, Y.; Wu, Y. *Chem. Commun.* **2012**, *48*, 8273–8275. doi:10.1039/c2cc31651j
- Kobayashi, Y.; Yamamoto, K.; Kumadaki, I. *Tetrahedron Lett.* **1979**, *20*, 4071–4072. doi:10.1016/S0040-4039(01)86506-0
- Urata, H.; Fuchikami, T. *Tetrahedron Lett.* **1991**, *32*, 91–94. doi:10.1016/S0040-4039(00)71226-3
- Chen, Q.-Y.; Duan, J.-X. *J. Chem. Soc., Chem. Commun.* **1993**, 1389–1391. doi:10.1039/C39930001389
- Kim, J.; Shreeve, J. M. *Org. Biomol. Chem.* **2004**, *2*, 2728–2734. doi:10.1039/b412480b
- Dubinina, G. G.; Furutachi, H.; Vivic, D. A. *J. Am. Chem. Soc.* **2008**, *130*, 8600–8601. doi:10.1021/ja802946s
- Dubinina, G. G.; Ogikubo, J.; Vivic, D. A. *Organometallics* **2008**, *27*, 6233–6235. doi:10.1021/om800794m
- Kawai, H.; Furukawa, T.; Nomura, Y.; Tokunaga, E.; Shibata, N. *Org. Lett.* **2011**, *13*, 3596–3599. doi:10.1021/ol201205t
- Chu, L.; Qing, F.-L. *J. Am. Chem. Soc.* **2010**, *132*, 7262–7263. doi:10.1021/ja102175w
- Chu, L.; Qing, F.-L. *Org. Lett.* **2010**, *12*, 5060–5063. doi:10.1021/ol1023135
- Chu, L.; Qing, F.-L. *J. Am. Chem. Soc.* **2012**, *134*, 1298–1304. doi:10.1021/ja209992w
- Jiang, X.; Chu, L.; Qing, F.-L. *J. Org. Chem.* **2012**, *77*, 1251–1257. doi:10.1021/jo202566h
- Chu, L.; Qing, F.-L. *Org. Lett.* **2012**, *14*, 2106–2109. doi:10.1021/ol300639a
- Wu, X.; Chu, L.; Qing, F.-L. *Angew. Chem., Int. Ed.* **2013**, *52*, 2198–2202. doi:10.1002/anie.201208971
- Zhao, T. S. N.; Szabó, K. J. *Org. Lett.* **2012**, *14*, 3966–3969. doi:10.1021/ol3017287
- Miyake, Y.; Ota, S.; Shibata, M.; Nakajima, K.; Nishibayashi, Y. *Chem. Commun.* **2013**, *49*, 7809–7811. doi:10.1039/c3cc44434a

License and Terms

This is an Open Access article under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/2.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The license is subject to the *Beilstein Journal of Organic Chemistry* terms and conditions: (<http://www.beilstein-journals.org/bjoc>)

The definitive version of this article is the electronic one which can be found at: [doi:10.3762/bjoc.9.322](http://dx.doi.org/10.3762/bjoc.9.322)