Novel Generation of 3,3,3-Trifluoropropynyllithium and Transformation of the Carbonyl Adducts to Trifluoromethyl-Substituted Allenes

Masaki Shimizu,* Masahiro Higashi, Youhei Takeda, Guofang Jiang, Masahito Murai, Tamejiro Hiyama

Department of Material Chemistry, Graduate School of Engineering, Kyoto University Katsura, Nishikyo-ku, Kyoto 615-8510, Japan
Fax +81(75)3832445; E-mail: shimizu@npc05.kuic.kyoto-u.ac.jp

Received 2 February 2007

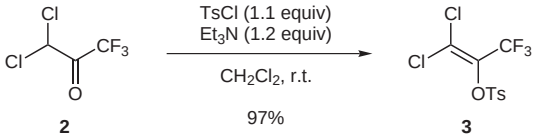
Abstract: A novel method for the generation of 3,3,3-trifluoropropynyllithium is reported, which involves treatment of trifluoromethyl-substituted enol tosylate, prepared from 1,1-dichloro-3,3,3-trifluoroacetone, with two equivalents of butyllithium. Palladium-catalyzed coupling reaction of sulfonates of the carbonyl adducts with organozinc reagents gave trifluoromethyl-containing tri- and tetrasubstituted allenes.

Key words: alkynes, allenes, fluorine, lithium, palladium

Since trifluoromethyl-containing compounds have found diverse applications in pharmaceutical, agrochemical, and materials sciences, development of facile synthetic methods for the preparation of trifluoromethylated compounds is one of the significant issues in organic synthesis.[1] 3,3,3-Trifluoropropynylated compounds serve as versatile building blocks for trifluoromethylated target molecules, because diverse synthetic transformations of a carbon–carbon triple bond are available.[2] For example, trifluoromethylated benzofurans,[2a] sugars,[2b] isoquinolines,[2d] and pyrazoles[2g] were synthesized starting from 3,3,3-trifluoropropynylated compounds. To incorporate a 3,3,3-trifluoropropynyl group into an organic compound, 3,3,3-trifluoropropynyllithium (**1**) is widely used.[3] Although **1** is efficiently generated by deprotonation of 3,3,3-trifluoropropyne (bp –48 °C) with butyllithium, treatment of 2-bromo-3,3,3-trifluoropropene (bp 33 °C), or 1,1,1,3,3-pentafluoropropane (bp 15 °C) with LDA, and by treatment of (*Z*)-2,3,3,3-tetrafluoro-1-iodoprop-1-ene with butyllithium, these protocols have to use volatile starting materials or require multistep transformation from commercially available 2,2,3,3,3-pentafluoropropan-1-ol in the case of the last procedure. Thus, facile method of the generation is desired in view of easy handling and convenience. In continuing our synthetic research on trifluoromethylated molecules utilizing 1,1-dichloro-3,3,3-trifluoroacetone (**2**) as a C3-building block,[4] we turned our attention to the generation of **1** from **2**. We report herein that novel generation and carbonyl addition of **1**. In addition, synthetic transformation of the carbonyl adducts to trifluoromethyl-substituted allenes is also demonstrated.

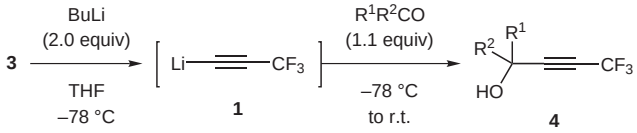
SYNLETT 2007, No. 7, pp 1163–1165
Advanced online publication: 13.04.2007
DOI: 10.1055/s-2007-977422; Art ID: Y00307ST

At first, acetone **2** was converted into enol tosylate **3** in 97% yield by treatment with *p*-toluenesulfonyl chloride in the presence of triethylamine (Equation 1).[5] Tosylate **3** was easily isolated by distillation under reduced pressure (bp 122 °C/2 Torr) and the gram-scale preparation was possible.[5]



Equation 1 Preparation of enol tosylate **3**

A THF solution of **3** (1.0 equiv) was treated with 2.0 equivalents of butyllithium at –78 °C. To the solution was added an aldehyde or ketone (1.1 equiv) at –78 °C and the resulting solution was allowed to warm to room temperature before quenching with aqueous NH_4Cl solution (Equation 2).[6] The results are shown in Table 1. Aromatic and aliphatic aldehydes as well as ketones produced propargylic alcohols **4** in good to excellent yields. Thus, it is apparent that the present protocol is a facile and efficient method for the generation of **1**.



Equation 2 Generation and carbonyl addition of **1**

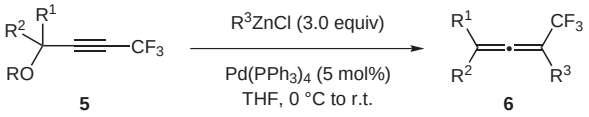
In order to examine the synthetic utility of **4**, we carried out palladium-catalyzed coupling reaction of propargyl sulfonates **5** derived from **4** with organozinc reagents to synthesize trifluoromethyl-substituted allenes, preparation of which remains unexplored.[7,8] Alcohols **4a**,**b**,**g** were converted into tosylates **5a**,**b**,**g** (Table 2, entries 1, 2, and 6), while sterically hindered tertiary alcohols **4e**,**h** were mesylated to afford **5e**,**h** (Table 2, entries 5 and 7).[9] Coupling reaction of **5a** with PhZnCl prepared from PhMgBr and $ZnCl_2$·TMEDA in the presence of $Pd(PPh_3)_4$ (5 mol%) gave **6a** in low yield due probably to the instability of **5a** (Table 2, entry 1). Meanwhile, phenylated allenes **6b**,**e**,**g**,**h** were produced under the same conditions and isolated by column chromatography on silica gel in moderate to good yields (entries 2, 5–7).[10] Trimethylsilylmethylzinc chloride also reacted with **5b** and **5h** in the

Table 1 Carbonyl Addition of **1**[a]

Entry	R^1	R^2	**4**	Yield (%)[b]
1	Ph	H	**4a**	97
2	$Ph(CH_2)_2$	H	**4b**	95
3	*c*-Hex	H	**4c**	92
4	(*E*)-PhCH=CH	H	**4d**	71
5	Ph	Ph	**4e**	92
6	Ph	Me	**4f**	88
7	Ph	CF_3	**4g**	84
8	$–(CH_2)_5–$		**4h**	72

[a] Compound **3** (1.0 equiv), BuLi (1.6 M in hexane, 2.0 equiv), R^1R^2CO (1.1 equiv), THF, –78 °C.
[b] Isolated yield.

presence of a catalytic amount of $Pd(PPh_3)_4$ to give silylmethylated allenes **6b′**,**h′** (entries 3 and 8). When **4b** was treated with Et_2Zn under the conditions, hydride incorporation took place giving rise to **6b″** in good yield (entry 4), which could be reasonable by assuming that β-elimination of an ethyl group on a Pd complex, generated by oxidative addition of a Pd catalyst into **4b** followed by transmetallation with Et_2Zn, and subsequent reductive elimination of the hydride complex.



Equation 3 Pd-catalyzed coupling reaction of **5** with organozinc reagents

Table 2 Preparation and Coupling Reaction of **5**[a]

Entry	**4**	R	**5**	Yield (%)[b]	R^3	**6**	Yield (%)[b]
1	**4a**	Ts	**5a**	91	Ph	**6a**	21
2	**4b**	Ts	**5b**	95	Ph	**6b**	69
3					CH_2SiMe_3	**6b′**	31
4					H[c]	**6b″**	86
5	**4e**	Ms	**5e**	63	Ph	**6e**	94
6	**4g**	Ts	**5g**	60	Ph	**6g**	42
7	**4h**	Ms	**5h**	84	Ph	**6h**	69
8					CH_2SiMe_3	**6h′**	61

[a] Preparation of **5**: **4** (1.0 equiv), TsCl (1.1 equiv), DMAP (5 mol%), Et_3N (1.2 equiv), CH_2Cl_2, 0 °C to r.t. Coupling reaction of **5**: compound **5** (1.0 equiv), R_3ZnCl (3.0 equiv), $Pd(PPh_3)_4$ (5 mol%), THF, r.t.
[b] Isolated yield.
[c] Et_2Zn was used instead of R^3ZnCl.

In summary, we have developed a facile two-step method for the generation of 3,3,3-trifluoropropynyllithium starting from DCTFA, which is applicable to gram-scale preparation of 3,3,3-trifluoropropynylated carbinols. Sulfonates of the carbonyl adducts can be transformed into trifluoromethyl-containing tri- and tetrasubstituted allenes conveniently via palladium-catalyzed cross-coupling reaction with organozinc reagents.

Acknowledgment

This work was supported by Grant-in-Aid for Creative Scientific Research, No 16GS0209, from Ministry of Education, Culture, Sports, Science, and Technology, Japan. The authors thank Central Glass Co Ltd. for the generous gift of 1,1-dichloro-3,3,3-trifluoroacetone.

References and Notes

(1) (a) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123. (b) *Fluorine-Containing Molecules: Structure, Reactivity, Synthesis, and Applications*; Liebman, J. F.; Greenberg, A.; Dolbier, W. R. Jr., Eds.; VCH: Weinheim, **1988**, 1. (c) Begue, J.-P.; Bonnet-Delpon, D. *Tetrahedron* **1991**, *47*, 3207. (d) McClinton, M. A.; McClinton, D. A. *Tetrahedron* **1992**, *48*, 6555. (e) Banks, R. E.; Smart, B. E.; Tatlow, J. C. *Organofluorine Chemistry: Principles and Commercial Applications*; Plenum Press: New York, **1994**. (f) *Chemistry of Organic Fluorine Compounds II: A Critical Review*; Hudlicky, M.; Pavlath, A. E., Eds.; ACS Monograph 187, American Chemical Society: Washington/DC, **1995**. (g) Hiyama, T. *Organofluorine Compounds – Chemistry and Applications*; Springer: Berlin, **2000**. (h) Shimizu, M.; Hiyama, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 214.

(2) (a) Yoneda, N.; Matsuoka, S.; Miyaura, N.; Fukuhara, T.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2124. (b) Yamazaki, T.; Mizutani, K.; Kitazume, T. *J. Org. Chem.* **1995**, *60*, 6046. (c) Jeong, I. H.; Jeon, S. L.; Kim, B. T. *Tetrahedron Lett.* **2003**, *44*, 7213. (d) Chae, J.; Konno, T.; Ishihara, T.; Yamanaka, H. *Chem. Lett.* **2004**, *33*, 314. (e) Konno, T.; Daitoh, T.; Noiri, A.; Chae, J.; Ishihara, T.; Yamanaka, H. *Tetrahedron* **2005**, *61*, 9391. (f) Konno, T.; Chae, J. H.; Miyabe, T.; Ishihara, T. *J. Org. Chem.* **2005**, *70*, 10172. (g) Hanamoto, T.; Egashira, M.; Ishizuka, K.; Furuno, H.; Inanaga, J. *Tetrahedron* **2006**, *62*, 6332.

(3) (a) Drakesmith, F. G.; Stewart, O. J.; Tarrant, P. *J. Org. Chem.* **1968**, *33*, 280. (b) Ref. 2b. (c) Katritzky, A. R.; Qi, M.; Wells, A. P. *J. Fluorine Chem.* **1996**, *80*, 145. (d) Brisdon, A. K.; Crossley, I. R. *Chem. Commun.* **2002**, 2420. (e) Konno, T.; Chae, J.; Kanda, M.; Nagai, G.; Tamura, K.; Ishihara, T.; Yamanaka, H. *Tetrahedron* **2003**, *59*, 7571.

(4) (a) Shimizu, M.; Fujimoto, T.; Minezaki, H.; Hata, T.; Hiyama, T. *J. Am. Chem. Soc.* **2001**, *123*, 6947. (b) Shimizu, M.; Fujimoto, T.; Liu, X.; Minezaki, H.; Hata, T.; Hiyama, T. *Tetrahedron* **2003**, *59*, 9811. (c) Liu, X.; Shimizu, M.; Hiyama, T. *Angew. Chem. Int. Ed.* **2004**, *43*, 879. (d) Shimizu, M.; Fujimoto, T.; Liu, X.; Hiyama, T. *Chem. Lett.* **2004**, *33*, 438. (e) Shimizu, M.; Jiang, G.; Murai, M.; Takeda, Y.; Nakao, Y.; Hiyama, T.; Shirakawa, E. *Chem. Lett.* **2005**, *34*, 1700.

(5) To a solution of **2** (13.6 g, 75 mmol) and *p*-toluenesulfonyl chloride (15.7 g, 82 mmol) in CH_2Cl_2 (100 mL) was added Et_3N (13.0 mL, 90 mmol) at r.t. After stirring at r.t. for 1 h,

the reaction mixture was diluted with Et_2O (50 mL). The resulting solution was washed with H_2O and then sat. NaCl aq solution, and dried over anhyd $MgSO_4$. Removal of organic solvent in vacuo followed by distillation under reduced pressure (122 °C/2 Torr) gave **3** (24.4 g, 97% yield) as a colorless oil. R_f = 0.33 (hexane–EtOAc, 10:1). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.49 (s, 3 H), 7.39 (d, *J* = 8.6 Hz, 2 H), 7.87 (d, *J* = 8.6 Hz, 2 H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 21.7, 119.1 (q, *J* = 275.5 Hz), 127.9, 128.3, 129.9, 132.4, 134.1 (q, *J* = 39.1 Hz). ^{19}F NMR (188 Hz, $CDCl_3$): δ = –63.1. IR (neat): 1618, 1394, 1196, 1153, 972 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 180 (10) [M^+ – Ts], 160 (12), 111 (33), 91 (23), 74 (100). Anal. Calcd for $C_{10}H_7Cl_2F_3O_3S$: C, 35.84; H, 2.11. Found: C, 36.3, H, 2.22.

(6) **Representative Procedure for Carbonyl Addition of 1**
To a THF solution of **3** (10.0 g, 30 mmol) was added BuLi (41 mL, 66 mmol, 1.6 M in hexane) at –78 °C. The solution was stirred at –78 °C for 10 min before the addition of 3-phenylpropanal (4.0 g, 30 mmol) in THF (20 mL) at –78 °C. The resulting solution was stirred at –78 °C for 1 h and then at r.t. for 1 h. The reaction mixture was quenched with sat. aq NH_4Cl solution (40 mL) at 0 °C and extracted with EtOAc (3 × 40 mL). The combined organic layer was dried over anhyd $MgSO_4$ and concentrated by rotary evaporator. The crude product was purified by column chromatography on silica gel (hexane–EtOAc, 15:1) to give **4b** (6.5 g, 95% yield, CAS No. 94792-93-5) as colorless oil.

(7) Review on transition-metal-catalyzed synthesis of allenes: (a) Ogasawara, M.; Hayashi, T. *In Modern Allene Chemistry*, Vol. 1; Krause, N.; Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, **2004**, 93. (b) Review on Pd-catalyzed cross-coupling reactions of propargylic compounds: Tsuji, J.; Mandai, T. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2589.

(8) Yamazaki and coworkers reported three-step transformation of alcohols **4** into trifluoromethyl-containing allenes CF_3–CHC=C=CR^1R^2. See: (a) Yamazaki, T.; Yamamoto, T.; Ichihara, R. *J. Org. Chem.* **2006**, *71*, 6251. Examples of trifluoromethyl-substituted allenes: (b) Bosbury, P. W. L.; Fields, R.; Haszeldine, R. N.; Moran, D. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1173. (c) Bosbury, P. W. L.; Fields, R.; Haszeldine, R. N. *J. Chem. Soc., Perkin Trans. 1* **1978**, 422. (d) Hanzawa, Y.; Kawagoe, K.-i.; Yamada, A.; Kobayashi, Y. *Tetrahedron Lett.* **1985**, *26*, 219. (e) Burton, D. J.; Hartgraves, G. A.; Hsu, J. *Tetrahedron Lett.* **1990**, *31*, 3699. (f) Konno, T.; Tanikawa, M.; Ishihara, T.; Yamanaka, H. *Chem. Lett.* **2000**, 1360. (g) Han, H. Y.; Kim, M. S.; Son, J. B.; Jeong, I. H. *Tetrahedron Lett.* **2006**, *47*, 209.

(9) **Representative Procedure for Preparation of Compounds 5**
To a solution of **4b** (1.5 g, 6.6 mmol), *p*-toluenesulfonyl chloride (1.4 g, 7.2 mmol), 4-dimethylaminopyridine (40 mg, 0.33 mmol) in CH_2Cl_2 (26 mL) was added Et_3N (1.1 mL, 7.9 mmol) at 0 °C. The resulting solution was stirred at r.t. for 2 h before quenching with sat. aq NH_4Cl solution (20 mL) at 0 °C. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic solvent was washed with sat. aq NaCl solution (60 mL), dried over anhyd $MgSO_4$ and concentrated in vacuo. The crude product was purified by silica gel column chromatography (hexane–EtOAc, 15:1) to give **5b** (2.4 g, 95% yield) as a colorless solid. Mp 48 °C. R_f = 0.45 (hexane–EtOAc, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.13–2.28 (m, 2 H), 2.46 (s, 3 H), 2.74–2.82 (m, 2 H), 5.07–5.11 (m, 1 H), 7.15 (d, *J* = 8.0 Hz, 2 H), 7.21–7.37 (m, 3 H), 7.35 (d, *J* = 8.4 Hz, 2 H), 7.80 (d, *J* = 8.4 Hz, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.5, 30.5, 36.3, 68.3, 74.3 (q, *J* = 52.9 Hz), 81.9 (q, *J* = 6.4 Hz), 113.2 (q, *J* = 257.9 Hz), 126.3, 127.9, 128.2, 128.4, 129.7, 132.7, 138.9, 145.5. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –51.8. IR (KBr): 2361, 2341, 1364, 1271, 1159, 746, 677 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 382 (1) [M^+], 210 (30), 141 (90), 91 (100). HRMS: *m/z* calcd for $C_{19}H_{17}F_3O_3S$ [M^+]: 382.0851; found: 382.0839.

(10) **Representative Procedure for the Preparation of Compounds 6**
To a solution of **5b** (0.10 g, 0.26 mmol) and $Pd(PPh_3)_4$ (15 mg, 0.013 mmol) in THF (2.6 mL) was added PhZnCl (0.79 mL, 0.79 mmol, 1.0 M in THF) at 0 °C. The solution was stirred at r.t for 2 h before quenching with sat. aq NH_4Cl solution (2 mL) at 0 °C. The aqueous layer was extracted with EtOAc (3 × 2 mL). The combined organic solvent was washed with sat. aq NaCl solution (6 mL), dried over anhyd $MgSO_4$, and concentrated by rotary evaporator. The crude product was purified by column chromatography on silica gel (hexane–EtOAc, 20:1) gave **6b** (52 mg, 69% yield) as colorless solid; mp 29 °C; R_f = 0.67 (hexane–EtOAc, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.54–2.67 (m, 2 H), 2.80–2.91 (m, 2 H), 5.96–6.01 (m, 1 H), 7.21–7.34 (m, 10 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 29.9, 34.9, 99.2, 102.1 (q, *J* = 34.5 Hz), 123.3 (q, *J* = 273.2 Hz), 126.1, 126.8, 126.8, 127.8, 128.4, 128.5, 129.8, 140.5, 204.0. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –60.9. IR (neat): 3030, 2926, 1497, 1303, 1168, 1121, 934, 694 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 288 (30) [M^+], 219 (20) [M^+ – CF_3], 129 (45), 91 (100). HRMS: *m/z* calcd for $C_{18}H_{15}F_3$ [M^+]: 288.1126; found: 288.1128.