Communications

Efficient and General One-pot Synthesis of β-Chloro-β-trifluoromethylated Enones from 3,3,3-Trifluoropropyne

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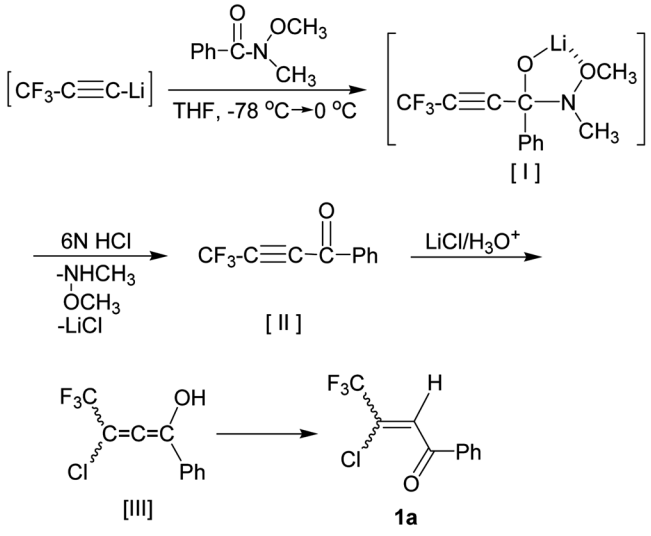
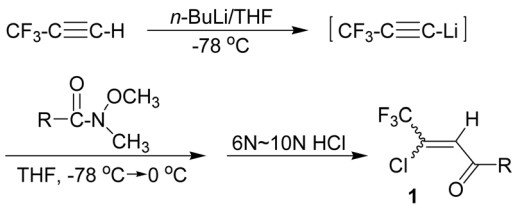
Trifluoromethylated compounds which can be easily transformed to other functionality have been receiving much attention as building blocks because of their potential to give a variety of trifluoromethylated analogs of bioactive and material molecules.[1-3] Especially, β-chloro-β-trifluoromethylated enones are very useful building blocks to provide trifluoromethyl substituted heterocycles such as pyrazoles, isoxazoles and pyrimidines.[4-7] Several methods for the preparation of β-chloro-β-trifluoromethylated enones have been reported in the previous literatures,[6,8-9] but the previous methods have some drawbacks such as formation of regioisomers, lack of generalization and low yield preparation. Eguchi et al. reported that addition of 1,1,1-trichloro-2,2,2-trifluoroethane to carbon-carbon double bond of trimethylsilyl enol ethers in the presence of copper(I) chloride, followed by dehydrochlorination with triethylamine, afforded β-chloro-β-trifluoromethylated enones in moderate yields.[8] Vilsmeier reagent which was formed from the reaction of dimethylformamide with oxalyl chloride was reacted with trifluoromethylated 1,3-diketone[6] or ketone[9] to provide β-chloro-β-trifluoromethylated enones in moderate yield, along with other regioisomer. In this communication, we wish to describe an efficient and general one-pot synthesis of β-chloro-β-trifluoromethylated enones from 3,3,3-trifluoropropyne.

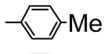
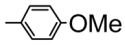
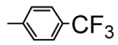
Recently, we reported that trifluoropropynyllithium was reacted with *N*-methoxy-*N*-methylbenzamide (Weinreb benzamide)[10] at −78 °C, followed by warming to 0 °C and quenching with water to give *E* and *Z* isomeric mixture of β-trifluoromethyl enaminone in good yield.[11] If the same reaction intermediate [I] would be treated with aqueous HCl, *N*-methoxy-*N*-methylamine formed in the reaction will be neutralized with HCl and thus chloride ion existed in the reaction mixture will react with β-trifluoromethylated ynone [II] to provide β-chloro-β-trifluoromethylated enones **1** *via* allenol [III] (Scheme 1). When trifluoropropynyllithium was reacted with Weinreb benzamide under the same reaction condition and then quenching with 3 N HCl, however, trifluoromethylated 1,3-diketone **2a** was obtained as an only product. The formation of **2a** can be postulated to be due to the reaction of ynone [II] with H_2O first instead of chloride ion under dilute acidic condition. This result indicates that concentration of 3 N HCl may not be enough to give **1a** and thus we decided to increase the concentration of HCl. Treatment of intermediate [I] with 6 N HCl resulted in the formation of **1a** in 95% yield as *E* and *Z* isomeric mixture (*E*/*Z* = 54/46). A longer reaction time with higher concentration than 6 N HCl afforded the same result. Assignment of *E* and *Z* isomers of **1a** was made by the comparison of chemical shift of authentic sample in ^{19}F and ^{1}H NMR spectroscopy.[8] Weinreb benzamides having substituent such as methyl, methoxy, fluoro, chloro, bromo and trifluoromethyl group on *para* position of benzene ring also provided the corresponding enones **1b-1g** in 92-94% yields under the same reaction condition. However, the use of 10 N HCl was required to give the corresponding enones **1h-1n** in the case of Weinreb benzamides having substituent on *ortho* or *meta* position of benzene ring, Weinreb naphthalenamide and Weinreb furanamide. Weinreb cyclohexanamide also afforded the corresponding enone **1o** in 81% yield. Results of these reactions are summarized in Table 1.



Scheme 1

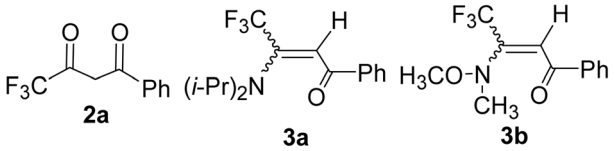
Table 1. Preparation of β-chloro-β-trifluoromethylated enones **1**



Compound No.	R	Yield (%)[a]	*E/Z*[b]
1a		95	54/56
1b		92	54/46
1c		94	50/50
1d		94	54/46
1e		92	55/45
1f		94	55/45
1g		92	53/47
1h		95	54/46
1i		90	54/46
1j		92	53/47
1k		90	54/46
1l		93	52/48
1m		88	54/46
1n		90	50/50
1o		81	54/46

[a]Isolated yield. [b]*E/Z* ratio was determined by ^{19}F NMR spectroscopy.

Since trifluoropropynyllithium can also be generated from 2-bromo-3,3,3-trifluoropropene,[12] we examined the hydrochlorination reaction of [I]. Therefore, the reaction of 2-bromo-3,3,3-trifluoropropene (1 equiv) with LDA (2 equiv) at –78 °C afforded trifluoropropynyllithium which was reacted with Weinreb benzamide to give intermediate [I]. However, the treatment of intermediate [I] with 6 N HCl resulted in the formation of **2a** in 80% yield. Previous literature[11] showed that treatment of [I] with H_2O in the presence of diisopropylamine resulted in the formation of enaminone **3a** exclusively. Enaminone **3a** was easily hydrolyzed to give **2a** at room temperature under 6 N HCl condition, whereas enaminone **3b** was hydrolyzed to give **2a** at 60 °C for 5 h under 6 N HCl condition. Therefore, a plausible mechanism for the formation of **2a** in this reaction may involve the addition reaction of diisopropylamine formed in the reaction process towards ynone [II] to give enaminone **3a** which was easily hydrolyzed under acidic condition.



A typical reaction procedure for the preparation of **1c** is as follows. A 25 mL two-neck round bottom flask equipped with a magnetic stirrer bar, a septum and an argon tee connected to an argon source was charged with 3,3,3-trifluoropropyne (0.564 g, 6.0 mmol) and THF at –78 °C and then *n*-BuLi (6.0 mmol) was added. After the reaction mixture was stirring at –78 °C for 30 min, 4,*N*-dimethoxy-*N*-methylbenzamide (0.585 g, 3 mmol) was added into the mixture at –78 °C and then slowly warmed to 0 °C, followed by quenching with 6 N HCl. The reaction mixture was extracted with diethyl ether twice. The diethyl ether solution was dried over anhydrous $MgSO_4$ and chromatographed on SiO_2 column. Elution with a mixture of hexane and ethyl acetate (10 : 1) provided 0.744 g of **1c** in 94% yield. *(Z)*-**1c**: oil: ^{1}H NMR ($CDCl_3$) δ 7.91 (d, J = 8.7 Hz, 2H), 7.40 (s, 1H), 6.99 (d, J = 8.7 Hz, 2H), 3.90 (s, 3H); *(E)*-**1c**: δ 7.89 (d, J = 8.7 Hz, 2H), 7.00 (s, 1H), 6.99 (d, J = 8.7 Hz, 2H), 3.90 (s, 3H): ^{19}F NMR ($CDCl_3$, internal standard $CFCl_3$) δ –65.67 (s, 3F, *E*-isomer), –70.40 (s, 3F, *Z*-isomer); MS, m/z (relative intensity) 266 (M^++2, 23), 264 (M^+, 70), 238 (18), 236 (54), 135 (100), 107 (12), 92 (14), 77 (16); IR (neat) 3046, 3020, 2968, 2940, 2845, 1675, 1598, 1575, 1510, 1462, 1445, 1260, 1180, 1150, 834 cm^{-1}. Anal. Calcd for $C_{10}H_6ClF_3O$: C, 50.00; H, 3.05. Found: C, 49.93; H, 2.99.

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References

1. Liebman, J. F.; Greenberg, A.; Dolbier, W. R. Jr. *Fluorine-Containing Molecules*; VCH: New York, 1988.
2. Banks, R. E.; Smart, B. E.; Tatlow, J. C. *Organofluorine Chemistry-Principle and Commercial Applications*; Plenum: New York, 1994.
3. Ojima, I.; McCarthy, J. R.; Welch, J. T. *Biomedical Frontiers of Fluorine Chemistry*; ACS: Washington, DC, 1996.
4. Alvernhe, G.; Langlois, B.; Laurent, A.; Le Drean, I.; Selmi, A. *Tetrahedron Lett.* **1991**, *32*, 643-646.
5. Alvernhe, G.; Greif, D.; Langlois, B.; Laurent, A.; Le Drean, I.; Pulst, M.; Selmi, A.; Weissenfels, M. *Bull. Soc. Chim. Fr.* **1994**, *131*, 167-171.
6. Arnaud, R.; Bensadat, A.; Ghobsi, A.; Laurent, A.; Le Drean, I.; Lesniak, S.; Selmi, A. *Bull. Soc. Chim. Fr.* **1994**, *131*, 844-853.
7. Diab, J.; Laurent, A.; Le Drean, I. *J. Fluorine Chem.* **1997**, *84*, 145-147.
8. Okano, I.; Uekawa, T.; Eguchi, S. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2575-2579.
9. Selmi, A.; Gaied, M. M. El; Alvernhe, G. *J. Fluorine Chem.* **1995**, *72*, 1-7.
10. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815-3818.
11. Jeong, I. H.; Jeon, S. L.; Min, Y. K.; Kim, B. T. *Tetrahedron Lett.* **2002**, *43*, 7171-7174.
12. Yamazaki, T.; Mizutani, K.; Kitazume, T. *J. Org. Chem.* **1995**, *60*, 6046-6056.