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Tributyl(3,3,3-trifluoro-1-propynyl)stannane as an efficient reagent for the preparation of various trifluoromethylated heterocyclic compounds

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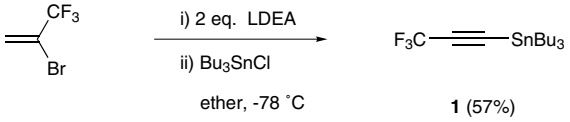
Abstract—Tributyl(3,3,3-trifluoro-1-propynyl)stannane was readily synthesized from 2-bromo-3,3,3-trifluoropropene in one step. The 1,3-dipolar cycloaddition of the stannane with diazomethane, phenylazide, and acetonitrile oxide smoothly proceeded to give the corresponding (tributylstannyl)trifluoromethyl-pyrazole, -triazole, and -isoxazole in good yields, respectively. These heterocyclic compounds are proved to be useful building blocks for the regioselective introduction of a functional group such as an aryl group or iodine.

Fluorinated heterocyclic compounds have recently received much attention due to their unique potential for pharmaceuticals and agrochemicals.[1] For instance, Celecoxib bearing a trifluoromethyl substituent on the pyrazole-ring shows anti-inflammatory and analgetic activity without the undesirable side effects associated with other non-steroidal anti-flammatories.[2] As the facile introduction of fluorine(s) into heterocyclic rings has still been limited, the development of new practical methods for their construction remains a formidable task. As a part of our study on the preparation of fluorinated building blocks,[3] we focused on the synthesis of useful fluorinated five-membered heterocyclic compounds. To this end, the 1,3-dipolar cycloaddition reactions especially should provide a convenient route to various five-membered heterocyclic structures. Although there are some reports on the synthesis of trifluoromethylated heterocycles by using various trifluoromethylated alkynes and 1,3-dipoles, no useful functional groups was embedded in those trifluoromethylated alkynes.[4] Consequently, further elaboration of the resultant 1,3-adducts has been limited. On the other hand, organostannane derivatives have been utilized as powerful reagents for construction of a variety of organic compounds.[5] On the basis of these consideration, we expected that the use of tributyl(3,3,3-trifluoro-1-propynyl)stannane (**1**) as a dipolarophile should give the corresponding highly potential five-membered heterocyclic adducts. We report herein a facile one step synthesis of **1**, its reaction with various 1,3-dipoles, and the useful transformations of the resulting trifluoromethylated stannylheterocycles.

Our initial study paid attention to the facile preparation of **1**. Because the reported method was far from practical, and as a result no synthetic applications were investigated.[6] One possible procedure for the synthesis of **1** would be the stannylation of metal 3,3,3-trifluoropropylide. According to a slightly modified procedure reported by Yamazaki et al., lithium 3,3,3-trifluoropropylide was prepared from readily available 2-bromo-3,3,3-trifluoropropene.[7] The successive addition of chlorotributylstannane (Bu_3SnCl) to the solution afforded the desired product **1**.[8] Although **1** was less stable hydrolytically than its non-fluorinated tin analog, the purification using bulb-to-bulb distillation under reduced pressure worked well to give **1** as a pale yellow liquid (bp; 90–100 °C/0.5 mmHg) in 57% yield (Scheme 1).[9]



Scheme 1.

Keywords: Pyrazole; Triazole; Isoxazole; Stannyl acetylene; Trifluoromethyl compounds; 1,3-Dipolar cycloaddition; Cross-coupling reaction.

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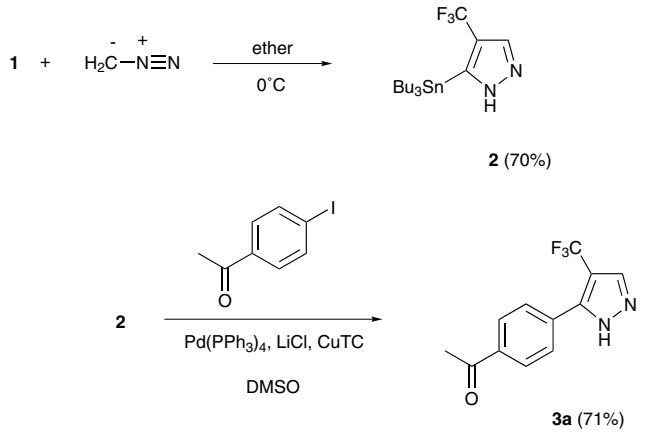


Scheme 2.

Initially, the addition of an ethereal solution of diazomethane to **1** at 0 °C for 1.5 h produced the corresponding trifluoromethylated stannylpyrazole (**2**) in 70% yield, exclusively (Scheme 2).[10] The structural assignment of this isomer was performed on the basis of the comparison of the corresponding ^{19}F chemical shift value in the literature.[11] The regioselectivity of the reaction can be explained in terms of HOMO–LUMO interactions as discussed in the literature.[12] The cycloaddition should be considered to be controlled by HOMO (diazomethane)–LUMO (**1**). The feasibility of the cross-coupling reaction of **2** with 4-iodoacetophenone as an aryl iodide was investigated under various conditions. The preliminary reaction under the standard conditions with Pd(0) catalysts and Cu(I) in DMF afforded no desired adducts. One reason for the difficulty of this cross-coupling reaction should be attributable to the sterically encumbered trifluoromethylated stannane. When we applied slightly modified conditions reported by Corey and co-workers,[13] this cross-coupling reaction smoothly proceeded to give the corresponding aryl(trifluoromethyl)pyrazole (**3a**) in 71% yield.[14]

Under the similar conditions, the cross-coupling reaction of **2** with 1-iodo-4-nitrobenzene also proceeded to give the corresponding pyrazole (**3b**) in 81% yield. Furthermore, introduction of iodine to the trifluoromethylated pyrazole ring was examined. 5-Iodo-4-(trifluoromethyl)pyrazole (**3c**) was readily prepared via room temperature iodination in 83% yield. The structures of two products are shown in Figure 1.

Secondly, the reaction between **1** and phenylazide was conducted in trimethylorthoformate for 36 h at 80–

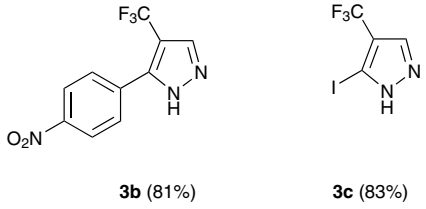
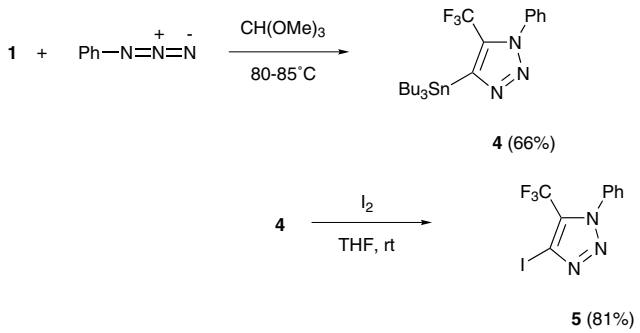


Figure 1. (4-Trifluoromethyl)pyrazoles.

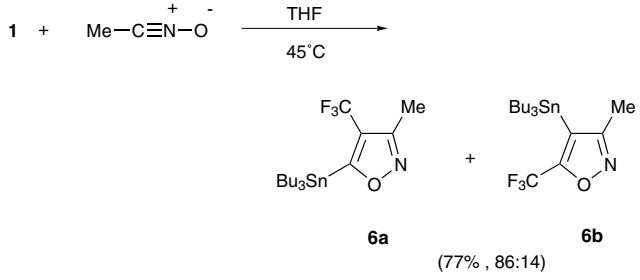


Scheme 3.

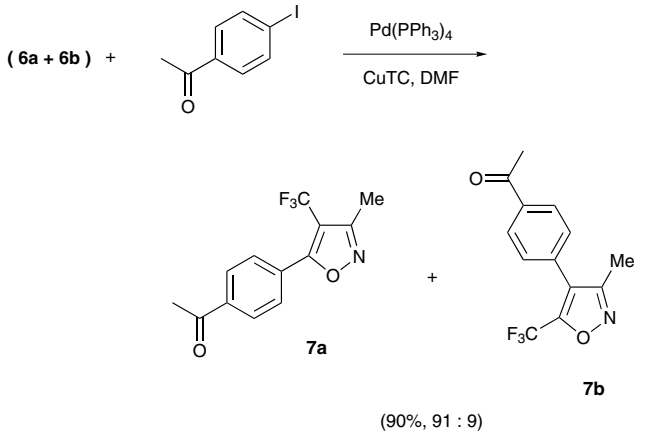
85 °C. The corresponding 1-phenyl-4-tributylstannyl-5-trifluoromethyl-1,2,3-triazole (**4**) was obtained in 66% yield, exclusively (Scheme 3).[15] The regioselective formation of the cycloadduct (**4**) suggests that the cycloaddition should be controlled by HOMO (phenylazide)–LUMO (**1**). The higher reaction temperature (above 90 °C) resulted in the contamination of another regioisomer.[4a] Iodination of **4** with iodine also provided the desired 4-iodo-1-phenyl-5-trifluoromethyl-1,2,3-triazole (**5**) in 81% yield, as shown in Scheme 3.

Finally, we have investigated the cycloaddition behavior of **1** with acetonitrile oxide as a representative nitrile oxide. In contrast to above dipoles, treatment of **1** with acetonitrile oxide generated in situ in THF at 45 °C for 12 h afforded the corresponding trifluoromethylated tributylstannyisoxazole (**6**) as an inseparable mixture of regioisomers in 77% combined yield (Scheme 4).[16] The structural assignment of these isomers was performed on the basis of the comparison of the corresponding ^{19}F chemical shift value in the literature.[4b,17] Attempts to improve this regioselectivity were unsuccessful at this stage.

The cross-coupling reaction of **6** with 4-iodoacetophenone was also examined under various conditions. Either of the isomers (**6a** and **6b**) underwent arylation giving the corresponding aryl(trifluoromethyl)isoxazole (**7**) with essentially the same regioisomeric ratio in 90% yield under the optimum conditions[18] (Scheme 5). Regioisomers of arylated isoxazole could be cleanly separated to each other. These coupling reactions required Cu(I) salt as a co-catalyst, and the use of Cu(I) thiophene-2-carboxylate (CuTC) under these conditions offered advantage over CuI.[19]



Scheme 4.



Scheme 5.

In summary, we have demonstrated the facile preparation of **1** and its usefulness for the construction of trifluoromethylated five-membered heterocyclic compounds via 1,3-dipolar cycloaddition reactions. Additional tributylstannyl groups on the heterocyclic rings have worked well for the regioselective introduction of various substituents into the rings. Further studies on their synthetic utility are now in progress in our laboratory.

Acknowledgements

We greatly thank F-Tech Co., Ltd for a gift of 2-bromo-3,3,3-trifluoropropene.

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8. Preparation of **1**: a 100 mL two-necked flask equipped with a magnetic stir bar, a stopcock and a three-way stopcock, was charged with diethylamine (0.6 mL, 5.8 mmol) and 10 mL of ether under argon. To the stirred mixture was dropwise added *n*-BuLi (1.56 M in hexane solution, 3.7 mL, 5.8 mmol) via syringe at 0 °C. After the addition was completed, the mixture was stirred for 10 min at this temperature. The mixture was cooled to −78 °C, then 2-bromo-3,3,3-trifluoropropene (0.27 mL, 2.6 mmol) was slowly added to the mixture. After an additional 10 min at −78 °C, Bu_3SnCl (0.67 mL, 2.5 mmol) was added dropwise at −78 °C, and the mixture was stirred for 30 min. To the resulting reaction mixture was successively added hexane (10 mL) and sodium sulfate decahydrate ($Na_2SO_4{\cdot}10H_2O$, ca. 10 g). After the mixture was dried over sodium sulfate, and filtered through a short silica gel column (ether as an eluent), the combined solution was concentrated in vacuo. The resulting oily residue was purified by bulb-to-bulb distillation (bath temp 90–100 °C/0.5 mmHg) to give the desired product (**1**) as pale yellow oil (0.548 g, 57%): IR (neat) 2175 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.92 (9H, t, J = 7.2 Hz), 1.07–1.14 (6H, m), 1.28–1.41 (6H, m), 1.53–1.63 (6H, m); ^{13}C NMR ($CDCl_3$): δ 11.3, 13.4, 26.7, 28,7, 94.6 (q, J = 52.8 Hz), 95.6 (q, J = 3.8 Hz), 112.7 (q, J = 257 Hz); ^{19}F NMR ($CDCl_3$): δ −51.2 (s); GC–MS *m/z* 326 [100, M^+−57 (Bu)]; Anal. Calcd for $C_{15}H_{15}F_3Sn$: C, 47.03; H, 7.10. Found: C, 46.71; H, 7.35.
9. During the course of our study, the different method for the preparation of **1** was reported, however their method required costly HFC-245fa (1,1,1-3,3-pentafluoropropane) and 3 equiv of *n*-butyllithium for the generation of the corresponding trifluoropropynyl anion: Brisdon, A. K.; Crossley, I. R.; Pritchard, R. G.; Sadiq, G.; Warren, J. E. *Organometallics* **2003**, *22*, 5534.
10. Data of **2**: colorless oil; ^1H NMR ($CDCl_3$, 270 MHz): δ 0.89 (9H, t, J = 7.3 Hz), 1.16–1.21 (6H, m), 1.27–1.39 (6H, m), 1.48–1.58 (6H, m), 7.87 (1H, s), 10.22 (1H, br s); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 10.27, 13.47, 27.12, 28.72, 120.61 (q, J = 35.9 Hz), 124.23 (q, J = 264 Hz), 137.40, 142.30; ^{19}F NMR ($CDCl_3$, 283 MHz): δ −55.91 (s); GC–MS *m/z* 367 (100); Anal. Calcd for $C_{16}H_{29}F_3N_2Sn$: C, 45.20; H, 6.88; N, 6.59. Found: C, 45.49; H, 6.79; N, 6.48.
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14. Data of **3a**: a white solid; mp 151.5–152.0 °C; IR (KBr) 3274, 1683 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz): δ 2.64 (3H, s), 7.74 (2H, d, J = 8.3 Hz), 7.91 (3H, s), 8.00 (2H, d, J = 8.3 Hz); ^{19}F NMR ($CDCl_3$, 283 MHz): δ −71.9 (s); GC–MS *m/z* 254 (M^+, 23), 239 (100); Anal. Calcd for $C_{12}H_9F_3N_2O$: C, 56.70; H, 3.57; N, 11.02. Found: C, 56.63; H, 3.55; N, 11.04.
15. Data of **4**: ^1H NMR ($CDCl_3$, 270 MHz): δ 0.90 (9H, t, J = 7.3 Hz), 1.21–1.27 (6H, m), 1.32–1.39 (6H, m), 1.56–1.58 (6H, m), 7.45–7.60 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 10.36 (d, J = 1.25 Hz), 13.51, 27.10, 28.75, 120.98 (q, J = 269 Hz), 125.51, 129.15, 130.14, 134.24 (q, J = 38.6 Hz), 136.03, 148.34 (q, J = 3.11 Hz); ^{19}F NMR ($CDCl_3$, 283 MHz): δ −56.60 (s); GC–MS *m/z* 444 (100); Anal. Calcd for $C_{21}H_{32}F_3N_3Sn$: C, 50.22; H, 6.42; N, 8.37. Found: C, 50.33; H, 6.40; N, 8.42.
16. Data of **6a**: ^1H NMR ($CDCl_3$, 270 MHz): δ 0.89 (9H, t, J = 7.3 Hz), 1.20–1.28 (6H, m), 1.28–1.36 (6H, m), 1.50–1.58 (6H, m), 2.38 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz): δ

9.51, 10.79, 13.40, 27.00, 28.56, 121.03 (q, $J = 36.5$ Hz), 123.04 (q, $J = 266$ Hz), 154.87 (overlapped, unclear); ^{19}F NMR ($CDCl_3$, 283 MHz): δ −57.63 (s) (major, **6a**), −62.74 (s) (minor, **6b**); GC–MS *m/z* 383 [49, M^+−57 (Bu)], [252 (100)]; Anal. Calcd for $C_{17}H_{30}F_3NOSn$: C, 46.39; H, 6.87; N, 3.18. Found: C, 46.51; H, 6.85; N, 3.20.

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18. Data of **7a**: a white solid; mp 84.0–85.0 °C; IR (KBr) 1694 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz): δ 2.47 (3H, q, $J = 1.5$ Hz), 2.66 (3H, s), 7.81 (2H, d, $J = 8.4$ Hz), 8.08 (2H, dq, $J = 8.4$, 1.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 10.92 (d, $J = 1.87$ Hz), 26.64, 107.8 (d, $J = 38.0$ Hz), 121.8 (q, $J = 268$ Hz), 128.49, 128.60 (q, $J = 1.87$ Hz), 129.73, 138.81, 158.40, 168.74 (q, $J = 3.11$ Hz), 196.97; ^{19}F NMR ($CDCl_3$, 283 MHz): δ −56.88 (s); GC–MS *m/z* 269 (M^+, 9), 254 (100); Anal. Calcd for $C_{13}H_{10}F_3NO_2$: C, 58.00; H, 3.74; N, 5.20. Found: C, 58.24; H, 3.72; N, 5.30.
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