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A novel approach to β-trifluoromethyl enaminones

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Abstract—β-Trifluoromethyl enaminones **1** were prepared in good yields from the reaction of trifluoropropynyl lithium with *N*-methoxy-*N*-methylbenzamide, followed by quenching with H_2O in the presence of a variety of amines. The use of hydrazine or benzamidine as an amine source in this reaction resulted in the formation of pyrazole **3** or pyrimidine **4**.

Considerable efforts have been made in the development of trifluoromethylated building blocks because of their potential to give new synthetic routes to a variety of trifluoromethylated compounds, some of which exhibit unique biological properties in the areas of agrochemicals, pharmaceuticals and material science.[1,2] In the course of our studies on the synthesis of trifluoromethylated compounds, we needed a facile and convenient synthetic route to β-trifluoromethyl enaminones, which are quite useful synthetic intermediates for the preparation of trifluoromethylated heterocyclic compounds. Recently, several researchers showed β-trifluoromethyl enaminones underwent amine exchange[3–6] with nucleophiles to give a variety of heterocyclic compounds as β-halo-β-trifluoromethyl enones did.[7–9] However, the previous methods for the preparation of β-trifluoromethyl enaminones have been quite limited and cannot be easily utilized. Sosnovskikh prepared β-trifluoromethyl enaminones from the reaction of methyl ketones with trifluoroacetonitrile in the presence of *N*-ethylanilino magnesium bromide.[10] The reactions of trifluorinated β-diketones with ammonium acetate and ammonium bicarbonate also afforded β-trifluoromethyl enaminones in a mixture of isomeric aminoenones.[11] Huang also synthesized β-trifluoromethyl enaminones from the treatment of *N*-aryl trifluoromethyl imidoyl iodides with methyl ketones in the presence of sodium hydride.[3] However, *N*-aryl trifluoromethyl imidoyl iodide[12] cannot be easily prepared via previous methods. Similarly, β-trifluoromethyl enaminones were prepared from the reaction of *N*-aryl trifluoromethyl imidoyl chloride with methyl ketones in the presence of LDA.[13] All of the previous methods had a lack of generality, low yield preparation and tedious procedure. Therefore, we wish to describe a novel and efficient method for the synthesis of β-trifluoromethyl enaminones.

Originally, we attempted to prepare β-trifluoromethylated ynone, which is not easily prepared via previous methods, from the reaction of trifluoropropynyl lithium with *N*-methoxy-*N*-methylbenzamide (Weinreb benzamide[14]). When trifluoropropynyl lithium generated from the reaction of trifluoropropyne[15] (1.1 equiv.) with *n*-BuLi (1.1 equiv.) was reacted with *N*-methoxy-*N*-methylbenzamide (1.0 equiv.) at −78°C followed by warming to 0°C and quenching with H_2O, however, an *E* and *Z* isomeric mixture (*E*/*Z*=13/87) of β-trifluoromethyl enaminone **1a** was obtained in 64% yield based on 60% conversion of *N*-methoxy-*N*-methylbenzamide. To consume *N*-methoxy-*N*-methylbenzamide completely, the same reaction was performed at −78°C followed by warming to room temperature and quenching with H_2O. However, only *N*-methoxy-*N*-methylbenzamide was recovered in 98% yield and no desired product was observed. It seems likely that the reaction was affected by temperature. Therefore, we decided to examine influence of temperature on the reaction. Treatment of trifluoropropynyl lithium (1.0 equiv.) with *N*-methoxy-*N*-methylbenzamide (1.1 equiv.) at −78°C followed by warming to −30°C and quenching with H_2O resulted in the formation of **1a** in 62% yield based on 27% conversion of *N*-methoxy-*N*-methylbenzamide. These experimental results indicate that equilibrium may occur in the reaction of trifluoropropynyl lithium

Keywords: trifluoropropynyl lithium; *N*-methoxy-*N*-methylbenzamide; β-trifluorormethyl enaminones.

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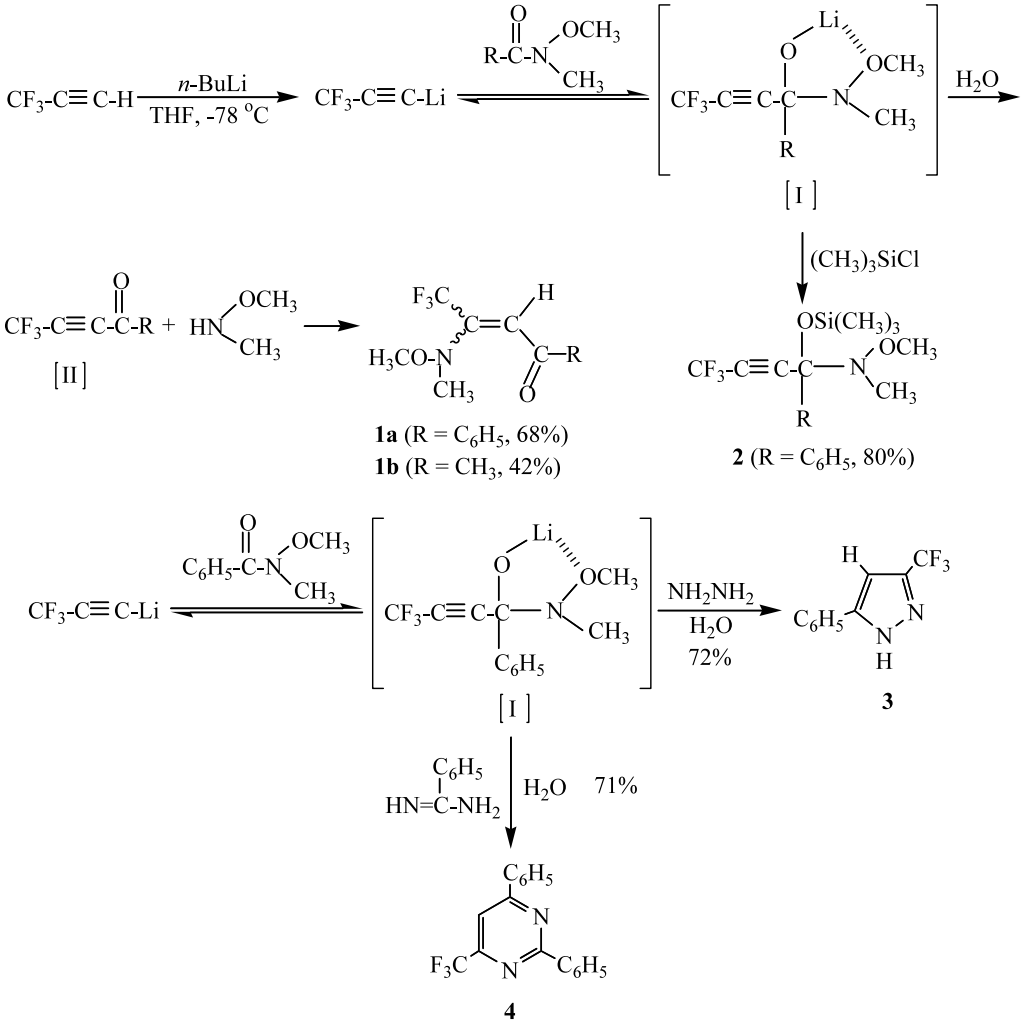
with *N*-methoxy-*N*-methylbenzamide to give addition intermediate [I]. To prove this possibility, a large excess of trifluoropropynyl lithium (4.0 equiv.) was used. Thus, the reaction of trifluoropropynyl lithium (4.0 equiv.) with *N*-methoxy-*N*-methylbenzamide (1.0 equiv.) at −78°C followed by warming to 0°C and quenching with H_2O, only desired product **1a** was obtained in 68% yield with no observation of *N*-methoxy-*N*-methylbenzamide. The use of *N*,*N*-dimethylbenzamide instead of *N*-methoxy-*N*-methylbenzamide under the optimized reaction conditions did not provide any desired product, but only starting material was recovered. Therefore, the *N*-methoxy group in Weinreb benzamide plays an important role to give lithium complex in intermediate [I]. *N*-Methoxy-*N*-methylacetamide as well as *N*-methoxy-*N*-methylbenzamide was also reacted with trifluoropropynyl lithium under the same reaction conditions to give the corresponding β-trifluoromethylated enamione **1b** in 42% yield. A plausible mechanism for the formation of **1a** seems likely that intermediate [I] was formed from the reaction of trifluoropropynyl lithium with Weinreb benzamide and then was reacted with H_2O to give ynone intermediate [II] which was rapidly reacted with *N*-methoxy-*N*-methylamine generated from the reaction to give **1a**. Trapping reaction of intermediate [I] with trimethylsilyl chloride afforded the corresponding siloxane derivative **2**[16] in 80% yield.

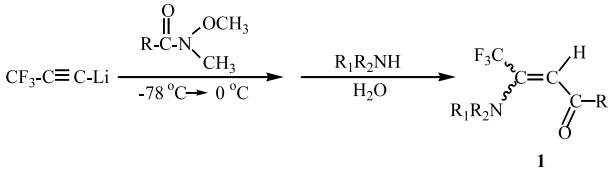
Although an unusual arylamino group exchange of enaminone with hydrazine or amidine to afford the corresponding pyrazole or pyrimidine has been reported in the previous literature,[3] *N*-methoxy-*N*-methylamino group exchange of **1a** with other amines has not been reported so far. When **1a** was reacted with piperidine at room temperature for 3 h in THF, only the *Z* isomer of piperidine-substituted enaminone **1c** was obtained in 98% yield. However, the reaction of **1a** with aniline under the same reaction conditions afforded only a trace amount of amine exchange product. The possible formation of ynone intermediate [II] and the result for the amine group exchange stimulated us to perform the quenching of intermediate [I] with H_2O in the presence of other types of amines. Therefore, treatment of intermediate [I] with H_2O in the presence of the same equivalence of piperidine at 0°C and then stirring at room temperature for 1 h resulted in the formation of **1c** (*Z* isomer only) in 85% yield. The similar reactions of intermediate [I] with *N*,*N*-dimethylamine, *N*-benzylmethylamine, benzylamine and morpholine provided the only *Z* isomer of corresponding enaminones **1d**, **1e**, **1f** and **1g** in 65–85% yields. The reaction of intermediate [I] with H_2O in the presence of aniline afforded the only *Z* isomer of the corresponding enaminone **1h** in 31% yield along with **1a** (*E*/*Z* = 13/87, 50% yield). It is postulated that the for-



mation of **1a** in this reaction could be due to the low reactivity of aniline toward ynone intermediate [II] as compare with *N*-methoxy-*N*-methylamine. The similar results were obtained from the reaction of intermediate [I] with H_2O in the presence of sterically hindered amines such as diisopropyl amine, 2,6-dimethylpiperidine, 2,2,6,6-tetramethylpiperidine, and hexamethyldisilazane. Especially, the reactions of intermediate [I] with 2,2,6,6-tetramethylpiperidine and hexamethyldisilazane did not provide any desired products **1k** and **1l**, but only **1a** was obtained in 60 and 61% yields, respectively. The experimental results are summarized in Table 1.

The assignment of *E* and *Z* isomers of **1a** was made by the comparison of chemical shift in ^{19}F NMR spectroscopy. It has been well established that ^{19}F NMR signal in the *Z* isomer of CF_3-trisubstituted vinylic compounds is more shielded than that in the *E* isomer.[17] Therefore, two singlet peaks at −65.97 and 61.84 ppm in the ^{19}F NMR spectrum are due to a CF_3 group in the *Z* and *E* isomers of **1a**, respectively. Determination of the configuration of **1a** was also supported by NOE observation (1.2%) between *N*-methyl group and the vinyl proton of (*E*)-**1a**, whereas no NOE observation was detected in (*Z*)-**1a**.

Table 1. Preparation of a variety of β-trifluoromethyl enaminones



1

Compound No.	R	R_1R_2NH	Yield(%)[a]	*E/Z*
1c			85	0/100
1d		$(CH_3)_2NH$	73	0/100
1e		$(Bn)CH_3NH$	81	0/100
1f		$Bn\text{-}NH_2$	65	0/100
1g			78	0/100
1h		$Ph\text{-}NH_2$	31[b]	0/100
1i		$[(CH_3)_2CH]_2NH$	55[c]	25/75
1j			74[d]	17/83
1k			0[e]	-
1l		$[(CH_3)_3Si]_2NH$	0[f]	-
1m			98	0/100
1n			76	0/100

[a]Isolated yield. [b]**1a** was obtained in 50% yield. [c]**1a** was obtained in 20% yield. [d]**1a** was obtained in 5% yield. [e]**1a** was obtained in 60% yield. [f]**1a** was obtained in 61% yield.

Treatment of intermediate [I] with H_2O in the presence of hydrazine or benzamidine also resulted in the formation of pyrazole **3**[18] or pyrimidine **4**[3] in 72 and 71% yields, respectively. No other regioisomer was observed in the formation of **3**.

A typical reaction procedure for the preparation of **1c** is as follows. A 25 mL two-neck round-bottomed flask equipped with a magnetic stirrer bar, septum and dry ice condenser connected to an argon source was charged with THF (10 mL) and then cooled to −78°C. After a dry ice condenser was filled with slush of dry ice and isopropyl alcohol, 3,3,3-trifluoropropyne (1.128 g, 12.0 mmol) was slowly added into flask by condensation via dry ice condenser. To a THF solution of 3,3,3-trifluoropropyne was added *n*-BuLi (12.0 mmol) at −78°C and the reaction mixture was stirred at −78°C for 0.5 h under argon atmosphere. *N*-Methoxy-*N*-methylbenzamide (0.495 g, 3.0 mol) was added into a mixture at −78°C and then warmed to 0°C. Piperidine (0.255 g, 3 mol) and H_2O (10 mL) were added into a mixture and then allowed to stir for 1 h at 0°C. The reaction mixture was extracted with ether twice. The ether solution was dried and chromatographed on SiO_2 column. Elution with a mixture of hexane and ethyl acetate (9:1) provided 0.722 g of **1c** in 85% yield. **1c**: oil; ^1H NMR ($CDCl_3$) δ 7.91–7.87 (m, 2H), 7.51–7.39 (m, 3H), 6.22 (s, 1H), 3.24 (s, 4H), 1.68 (s, 6H); ^{19}F NMR ($CDCl_3$) δ −64.46 (s, 3F); MS, *m*/*z* (relative intensity) 283 (M^+, 37), 266 (52), 131 (21), 105 (33), 103 (17), 91 (11), 83 (100), 77 (25), 69 (11); IR (neat) 3062, 2941, 1645, 1599, 1581, 1564, 1470, 1279, 1227, 1180, 1126, 1005, 1140, 771, 632 cm^{-1}. Anal. calcd for $C_{15}H_{16}F_3NO$: C, 63.60; H, 5.69. Found: C, 63.45; H, 5. 63%.

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16. **2**: oil; ^{1}H NMR ($CDCl_3$) δ 7.65–7.60 (m, 2H), 7.38–7.35 (m, 3H), 3.46 (s, 3H), 2.40 (s, 3H), 0.20 (s, 9H); ^{19}F NMR ($CDCl_3$) δ −51.20 (s, 3F); MS, m/z (relative intensity) 271 (M^+−60, 100), 242 (36), 208 (12), 179 (11), 151 (23), 105 (27), 77 (10), 73 (47); IR (neat) 3067, 2960, 2262, 1450, 1273, 1214, 1147, 1087, 1068, 1024, 892, 844 cm^{-1}. Anal. calcd for $C_{15}H_{20}F_3NO_2Si$: C, 54.36; H, 6.08. Found: C, 54.49; H, 5.99.
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