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Short communication

One pot synthesis of novel α,β-dichloro-β-trifluoromethylated enones and their application to the synthesis of trifluoromethylated heterocycles

Sung Lan Jeon [a], Joa Kyum Kim [a], Jang Bae Son [a], Bum Tae Kim [b], In Howa Jeong [a,*]

[a] *Department of Chemistry, Yonsei University, Wonju 220-710, South Korea*
[b] *Korea Research Institute of Chemical Technology, Daejeon 305-606, South Korea*

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Abstract

Trifluoropropynyllithium was reacted with 1 equiv of Weinreb benzamides in THF at −78 to 0 °C, followed by treatment with 4 equiv of trifluoromethanesulfonyl chloride to give α,β-dichloro-β-trifluoromethylated enones **1** in 61–68% yield. The reactions of **1a** with substituted amidines or hydrazines in refluxing 1,4-dioxane-CH_3CN afforded trifluoromethylated chloropyrimidines **3** and chloropyrazoles **6** in 58–98% yields. The microwave-assisted coupling reactions of **3** with substituted phenylstannane and allylstannane in refluxing CH_3CN in the presence of $Pd(PPh_3)_4$ provided the corresponding phenyl and allyl substituted pyrimidines **4** in 89–98% yields.

Keywords: Trifluoropropynyllithium; Trifluoromethanesulfonyl chloride; α,β-Dichloro-β-trifluoromethylated enones; Trifluoromethyl substituted heterocycles; Microwave-assisted coupling reaction

1. Introduction

The 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]. Among such building blocks, we are interested in the preparation of β-chlorinated β-trifluoromethyl enones which are very useful building blocks to provide trifluoromethyl substituted heterocycles, such as pyrazoles, isoxazoles and pyrimidines [4–7]. Although several methods for the preparation of β-chloro-β-trifluoromethylated enones and their application to the synthesis of heterocycles have been well documented in the previous literatures [6,8,9], however, there has been no report on the preparation of α,β-dichloro-β-trifluoromethylated enones. Advantage of this α,β-dichloro enones as compared to β-chloro enones in the synthetic point of view is to be able to utilize the chloro functionality on the ring after synthesis of heterocyclic compounds and thus extend the functionality of heterocyclic ring system. Herein, we wish to report the first preparation of novel α,β-dichloro-β-trifluoromethylated enones from trifluoropropyne and their application to the synthesis of pyrimidines and pyrazoles.

2. Results and discussion

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 then quenching with water to give a mixture of *E* and *Z* isomers of β-trifluoromethyl enaminone in good yield [11]. The reaction mechanism in this reaction seems likely the formation of lithium complex intermediate [I] which provided β-trifluoromethyl enaminone via the reaction of β-trifluoromethyl ynone with *N*-methoxy-*N*-methylamine formed in the reaction process. If the same intermediate [I] would be treated with trifluoromethanesulfonyl chloride (TfCl), trifluoromethanesulfonate ester derivative will be formed in the reaction mixture, which will be further reacted with chloride ion formed in the reaction process to give chloroallenyl amine derivative which might be utilized to give the α,β-dichloro-β-trifluoromethylated enones. Therefore, we began with the reaction of intermediate [I] with TfCl under the several reaction

* Corresponding author. Tel.: +82 33 760 2240; fax: +82 33 763 4323.
E-mail address: jeongih@yonsei.ac.kr (I.H. Jeong).

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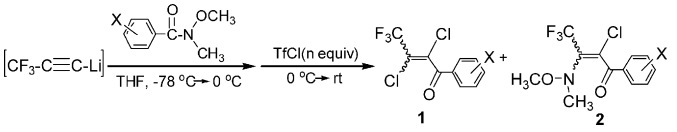
Table 1
Preparation of α,β-dichloro-β-trifluoromethylated enones **1**



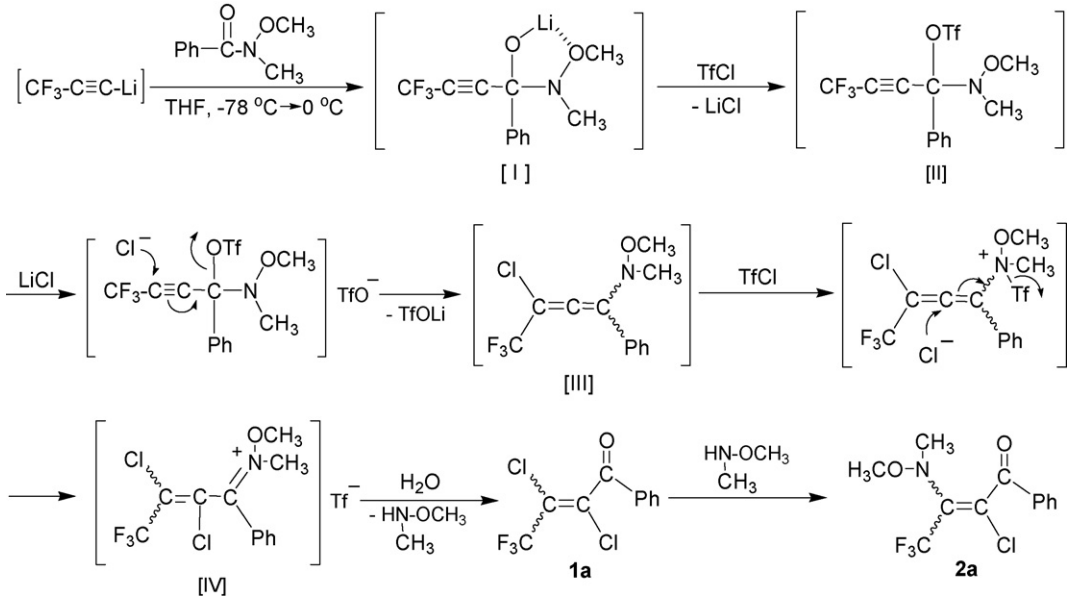
Compound no.	*X*	*n* (equiv)	Yield (%)[a,b]	
			1	**2**
1a, **2a**	H	1	–[c]	–[c]
1a, **2a**	H	2	40	38
1a, **2a**	H	3	52	26
1a, **2a**	H	4	65	16
1b, **2b**	*p*-Cl	4	63	15
1c, **2c**	*p*-CH_3	4	67	14
1d, **2d**	*p*-CF_3	4	68	16
1e, **2e**	*m*-Cl	4	61	17
1f, **2f**	*m*-CH_3	4	65	14

[a] Isolated yield.
[b] AII products are *E* and *Z* isomeric mixture.
[c] Reaction provided a messy reaction mixture which could not afford isolable products.

conditions. When intermediate [I] was reacted with 1 equiv of TfCl, a messy reaction mixture was obtained unexpectively. However, the treatment of [I] with 2 equiv of TfCl under the same reaction condition resulted in the formation of α,β-dichloro-β-trifluoromethylated enone **1a** (*E*/*Z* = 37/63) and α-chloro-β-trifluoromethylated enaminone **2a** (*E*/*Z* = 80/20) in 40 and 38% yields, respectively. The assignment of *E* and *Z* isomers of **1a** and **2a** 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 **1a** and **2a** is less shielded than that in the *E*-isomer by a strong anisotropic effect for the carbonyl bond to CF_3 group [8]. The use of higher equiv of TfCl in this reaction caused to increase the yield of **1a** and decrease the yield of **2a**. Thus, the highest yield (65%) of **1a** was obtained from the reaction of [I] with 4 equiv of TfCl, whereas **2a** was obtained in only 16% yield. Weinreb benzamides having substituent, such as chloro, methyl and trifluoromethyl group on *meta* or *para* position of benzene ring also provided the corresponding enones **1b–f** in 61–68% yields under the same reaction condition. However, treatment of [I] having R=CH_3 with TfCl resulted in the formation of a messy reaction mixture and thus the desired product was not obtained. The results of these reactions are summarized in Table 1.

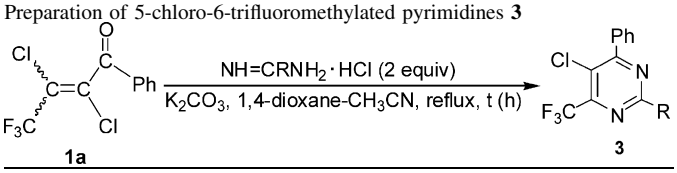
The reaction mechanism could involve the first formation of propargylic triflate [II], from the reaction of intermediate [I] with 1 equiv of TfCl, which is reacted with chloride ion formed in reaction process to give allene intermediate [III]. Intermediate [III] was further reacted with another 1 equiv of TfCl to give immonium ion [IV] which was hydrolyzed to give enone **1a**. It seems likely that enone **1a** is a reactive species toward nucleophiles and thus was reacted with (*N*-methoxy-*N*-methyl)amine formed in reaction process to give enaminone **2a**. Since the formation of **2a** depends on the amount of (*N*-methoxy-*N*-methyl)amine formed in reaction process, TfCl will suppress the formation of **2a** by trapping (*N*-methoxy-*N*-methyl)amine. A plausible mechanism for the formation of **1a** was shown in Scheme 1.

The cyclization reactions between **1a** and 2 equiv of amidine derivatives substituted by methyl, phenyl, amino, phenylamino and methyamino group in refluxing 1,4-dioxane-CH_3CN cosolvent were successful and 5-chloro-6-trifluoromethylated pyrimidine derivatives **3b–f** were obtained in 62–98% isolated yields. The use of 1,4-dioxane and CH_3CN as cosolvent was important in these reactions. Most reactions could be completed in 12–24 h depending on the substituent of amidine. However, amidine was not reacted with **1a** under several reaction conditions, such as refluxing in 1,4-dioxane, refluxing in 1,4-dioxane-H_2O or refluxing in 1,4-



Scheme 1. A plausible mechanism for the formation of α,β-dichloro-β-trifluoromethylated enone **1a**.

Table 2
Preparation of 5-chloro-6-trifluoromethylated pyrimidines **3**



1a **3**

Compound no.	*R*	*t* (h)	Yield (%)[a]
3a	H	24	NR[b]
3b	CH_3	18	98
3c	C_6H_5	12	95
3d	NH_2	12	81
3e	NHPh	18	58
3f	NHMe	18	62

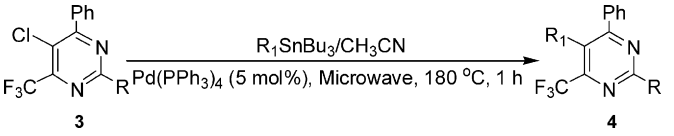
[a] Isolated yield.
[b] No reaction.

dioxane-CH_3CN. The results of these reactions are summarized in Table 2.

We also tested the coupling reaction of **3c** with phenylstannane in the presence of $Pd(PPh_3)_4$ catalyst. After several reaction conditions were examined, it was found that microwave-assisted coupling reaction in CH_3CN at 180 °C for 1 h afforded the coupling product **4a** in 93% isolated yield based on the 97% conversion of **3c**. The only small amount of reduced pyrimidine **5a** was observed. When the microwave-assisted coupling reaction of **3c** with phenylstannane was performed in the presence of 1 equiv of $Pd(PPh_3)_4$ and 1 equiv of CuI in DMF at 250 °C for 1 h, **4a** and **5a** were obtained in 38 and 58% isolated yields, respectively, based on the 60% conversion of **3c**. The coupling reaction of **3c** with phenylstannane under no microwave-assisted reaction condition did not progress at all and **3c** was recovered. Substituted phenylstannane and allylstannane were also undergo the coupling reaction with **3c** to give **4b–e** in 89–98% yields based on the 53–90% conversion of **3c** under the same reaction condition. The reaction between **3b** and phenylstannane and allylstannane also afforded the corresponding coupling products **4f–j** in 97–98% yields, but the conversion(35–48%) of **3b** was worse than **3c**. Amido substituted pyrimidine **3g** prepared from the reaction of **3d** with benzoly chloride in refluxing CH_2Cl_2 in the presence of pyridine was reacted with substituted phenylstannane and allylstannane under the same reaction condition provided the coupling products **4k–o** in 90–98% isolated yields based on the 100% conversion of starting material. A small amount of reduced pyrimidine was obtained in less than 5% yield for each case. The results of the coupling reaction were summarized in Table 3.

The cyclization reactions of **1a** with hydrazine derivatives were also successful and afforded the corresponding

Table 3
The coupling reaction of **3** with phenylstannane and allylstannane



3 **4**

Compound no.	*R*	R_1	Conversion of **3** (%)	Yield (%)[a]
4a	Ph	Ph	97	93
4b	Ph	*P*-FC_6H_4	90	89
4c	Ph	*p*-$CF_3C_6H_4$	70	98
4d	Ph	*p*-$MeOC_6H_4$	53	89
4e	Ph	CH_2=CH–CH_2	72	95
4f	Me	Ph	48	98
4g	Me	*p*-FC_6H_4	39	98
4h	Me	*p*-$CF_3C_6H_4$	35	98
4i	Me	*p*-$MeOC_6H_4$	38	97
4j	Me	CH_2=CH–CH_2	38	97
4k	NHC(O)Ph	Ph	100	92
41	NHC(O)Ph	*p*-FC_6H_4	100	95
4m	NHC(O)Ph	*p*-$CF_3C_6H_4$	100	98
4n	NHC(O)Ph	*p*-$MeOC_6H_4$	100	90
4o	NHC(O)Ph	CH_2=CH–CH_2	100	97

[a] Isolated yield.

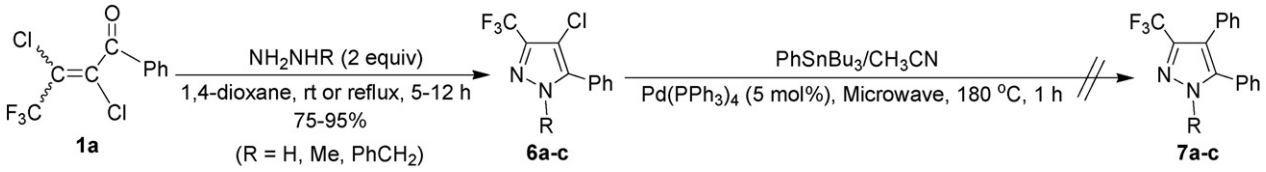
trifluoromethylated chloropyrazole derivatives **6a–c** in high yields (Scheme 2), but these products did not undergo the coupling reaction with phenylstannane reagent under microwave-assisted conditions.

3. Conclusion

In conclusion, we have developed an efficient one-pot synthesis of novel α,β-dichloro-β-trifluoromethylated enones and their reactions with substituted amidines and hydrazines afforded the corresponding trifluoromethylated chloropyrimidines and chloropyrazoles. The microwave-assisted coupling reactions of trifluoromethylated chloropyrimidines with phenylstannane or allylstannane in the presence of Pd catalyst provided the corresponding trifluoromethylated phenylpyrimidines or allylpyrimidines. Further study on transformations of chloro substituent in pyrimidine **3** and pyrazole **6** is in progress.

4. Experimental

^1H NMR spectra were recorded on a 200 MHz Gemini-200 NMR spectrometer and ^{19}F NMR spectra were recorded on a 100 MHz Bruker AC-100F NMR spectrometer with tetramethylsilane (TMS) and $CFCl_3$ as an internal standard, respectively, and the upfield as negative. All chemical shifts (δ) are expressed in parts per million and coupling constant (J)



1a **6a-c** **7a-c**

Scheme 2. Preparation of trifluoromethylated chloropyrazole derivatives **6a–c**.

are given in Hertz. Infrared spectra were determined on a Mattson Genesis series FT High Resolution Spectrophotometer. Mass spectra were obtained by using GC/MS-Qp1000-Shimadzu (EI, 70 eV). Melting points were determined in open capillary tubes and are unconnected.

Commercially available reagents were purchased from Aldrich, Lancaster, Tokyo Kasei and Fluorochem. All solvents were dried by general purification method. Flash chromatography was performed on 40–60 μm silica gel (230–400 mesh).

5. Representative experimental procedures

5.1. 2,3-Dichloro-4,4,4-trifluoro-1-phenyl-2-buten-1-one (*1a*)

A 25 mL two-neck round bottom flask equipped with a magnetic stirrer bar, a septum and nitrogen tee connected to an argon source was charged with 3,3,3-trifluoropropyne (1.128 g, 12.0 mmol) and THF at −78 °C and then *n*-BuLi (12.0 mmol) was added. After the reaction mixture was stirring at −78 °C for 30 min, *N*-methoxy-*N*-methylbenzamide (1.815 g, 11.0 mmol) was added into the mixture at −78 °C and then slowly warmed to 0 °C, followed by quenching with trifluoromethanesulfonyl chloride (7.37 g, 44.0 mmol). 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 (19:1) provided 1.909 g of **1a** (*E*/*Z* = 37/63) in 65% yield. **1a**: oil: ^{1}H NMR ($CDCl_3$) δ 7.97–7.87 (m, 2H), 7.75–7.65 (m, 1H), 7.60–7.50 (m, 2H): ^{19}F NMR ($CDCl_3$, internal standard $CFCl_3$) δ −63.43 (s, 3F, *E*-isomer), −62.86 (s, 3F, *Z*-isomer); MS, *m*/*z* (relative intensity) 270 (M^+ + 2, 1), 268 (M^+, 2), 217 (10), 105 (100), 77 (71), 69 (35); IR (neat) 3069, 1691, 1598, 1312, 1255, 1195, 1079 cm^{-1}. Anal. Calcd. for $C_{10}H_5Cl_2F_3O$: C, 44.64; H, 1.87. Found: C, 44.55; H, 1.85.

5.2. 5-Chloro-4-trifluoromethyl-2,6-diphenylpyrimidine (*3c*)

A 25 mL two-neck round bottom flask equipped with a magnetic stirrer bar, a septum and nitrogen tee connected to an argon source was charged with **1a** (0.135 g, 0.5 mmol) and 1,4-dioxane-CH_3CN. Bezamidine generated from the neutralization of benzamidine·HCl·H_2O (0.172 g, 1.1 mmol) with K_2CO_3 was added into the mixture and then the reaction was heated to reflux for 12 h. After quenching with water, 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 (9:1) provided 0.159 g of **3c** (*E*/*Z* = 37/63) in 95% yield. **3c**: mp 114–115 °C: ^{1}H NMR ($CDCl_3$) δ 8.55–8.49 (m, 2H), 7.95–7.86 (m, 2H), 7.61–7.44 (m, 6H); ^{19}F NMR ($CDCl_3$, internal standard $CFCl_3$) δ −67.91 (s, 3F); MS, *m*/*z* (relative intensity) 336 (M^+ + 2, 30), 334 (M^+, 89), 299 (49), 231 (14), 162 (53), 127 (38), 103 (100), 77 (29); IR (KBr) 3065, 2926, 1544, 1373, 1226, 1175, 1046 cm^{-1}. Anal. Calcd. for $C_{17}H_{10}ClF_3N_2$: C, 61.00; H, 3.01. Found: C, 60.87; H, 2.98.

5.3. 4-Trifluoromethyl-2,5,6-triphenylpyrimidine (*4a*)

A 2 mL microwave reactor was charged with **3c** (0.033 g, 0.1 mmol), $Pd(PPh_3)_4$ (5 mol%) and 1.5 mL of dry CH_3CN. After bubbling with air gas, phenylstannane (0.048 g, 0.13 mmol) was added into the reactor. The reactor was heated at 180 °C for 1 h. After quenching with 10% KF solution at room temperature, the reaction mixture was extracted with CH_2Cl_2 twice. The CH_2Cl_2 solution was dried over anhydrous $MgSO_4$ and chromatographed on SiO_2 column. Elution with a mixture of hexane and ethyl acetate (9:1) provided 0.035 g of **4a** in 93% yield. **4a**: mp 127–128 °C: ^{1}H NMR ($CDCl_3$) δ 8.68–8.59 (m, 2H), 7.57–7.49 (m, 3H), 7.42–7.17 (m, 10H); ^{19}F NMR ($CDCl_3$, internal standard $CFCl_3$) δ −63.30 (s, 3F); MS, *m*/*z* (relative intensity) 376 (M^+, 51), 375 (100), 355 (8), 168 (13), 151 (12), 77 (20); IR (KBr) 3062, 2929, 1554, 1402, 1196, 1144 cm^{-1}. Anal. Calcd. for $C_{23}H_{15}F_3N_2$: C, 73.40; H, 4.02. Found: C, 73.25; H, 4.08.

5.4. 4-Chloro-3-trifluoromethyl-N-methyl-5-phenylpyrazole (*6b*)

A 25 mL two-neck round bottom flask equipped with a magnetic stirrer bar, a septum and nitrogen tee connected to an argon source was charged with **1a** (0.135 g, 0.5 mmol) and 1,4-dioxane. Methylhydrazine (0.051 g, 1.1 mmol) was added into the mixture and then the reaction was stirred at room temperature for 5 h. After quenching with water, 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 (1:2) provided 0.137 g of **6b** in 95% yield. **6b**: oil: ^{1}H NMR ($CDCl_3$) δ 7.86–7.81 (m, 2H), 7.48–7.36 (m, 3H), 4.04 (s, 3H); ^{19}F NMR ($CDCl_3$, internal standard $CFCl_3$) δ −59.46 (s, 3F); MS, *m*/*z* (relative intensity) 262 (M^+ + 2, 14), 260 (M^+, 41), 191 (13), 167 (21), 149 (56), 125 (15), 111 (11), 97 (19), 83 (34), 69 (72), 57 (70), 43 (100); IR (neat) 3066, 2058, 1444, 1271, 1132, 1089 cm^{-1}. Anal. Calcd. for $C_{11}H_8ClF_3N_2$: C, 50.07; H, 3.01. Found: C, 49.91; H, 3.04.

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