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Reactions of novel trifluoromethyl propargylic carbocation with carbon nucleophiles

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Abstract—Trifluoromethyl propargylic carbocation [I] generated from the reaction of 1-amino substituted 3-trifluoromethyl-2-propynyl trimethylsilyl ether **1** with TMSOTf in CH_2Cl_2 at −15 °C, followed by warming to room temperature reacted with 1.2 equiv of substituted benzenes, RMgBr and allylsilane to give the enones **3a**–**l** and **5**, respectively. The reaction of [I] with anisole, followed by treatment with Grignard reagents afforded the corresponding allyl amine derivatives **7**, which underwent cyclization reaction to give indene derivatives **8** by using 2 equiv of TMSOTf.

The use of trifluoromethylated building block is essential for the synthesis of trifluoromethyl substituted molecules, which are very useful in the areas of pharmaceuticals, agrochemicals and material science.[1–3] Among such building blocks, trifluoromethyl propargylic moieties have been receiving increasing attention because of the transformations of triple bond functionality. For examples, trifluoromethyl propargylic alcohols[4–6] were utilized to give the corresponding allylic alcohols with high stereoselectivity via Red-Al or Lindlar catalyst reduction, in which allylic alcohols were transformed to provide chiral 2,6-dideoxy-6,6,6-trifluorosugars.[7,8] Trifluoromethyl propargylic alcohols were also reacted with ethyl orthoacetate under acidic condition to afford trifluoromethylated allene derivatives via Claisen rearrangement.[9] Trifluoromethylated allene derivatives were also obtained from the palladium-catalyzed coupling reaction of trifluoromethylated propargyl mesylates with organozinc reagents in the presence of a catalytic amount of $Pd(PPh_3)_4$.[10] In contrast to these synthetic utilities of trifluoromethylated propargylic building blocks, there has been a quite limited study of the reaction of trifluoromethyl propargylic carbocation with nucleophiles. The main reason for the limited study seems likely due to the unstability of trifluoromethyl propargylic carbocation species. However, Konno et al. reported recently that trifluoromethylated propargyl acetate was readily reacted with dicobaltoctacarbonyl to form the corresponding cobalt complex, in which dicobaltoctacarbonyl group effectively stabilizes trifluoromethyl propargylic carbocation.[11] In recent years, we have prepared 1,1,1-trifluoro-4-(*N*-methoxy-*N*-methyl)amino-1-trimethylsiloxy-1-phenyl-2-butyne (**1**) as a source of (trifluoromethyl)ethynylation reagent,[12] in which the (*N*-methoxy-*N*-methyl)amino group could compensate the destabilizing effect of trifluoromethyl group and thus enhance the stability of the trifluoromethyl propargylic carbocation. We report in this letter the formation and reactions of the relatively stable trifluoromethyl propargylic carbocation generated from the reaction of **1** with trimethylsilyl trifluoromethanesulfonate (TMSOTf).

Our initial studies began with the reaction of **1** with TMSOTf to figure out whether trifluoromethyl propargylic carbocation will be formed or not. Treatment of **1** with TMSOTf (1 equiv) in THF at −78 °C, followed by warming to room temperature and then quenching with H_2O resulted in the formation of trifluoromethylated enaminone **2** as a mixture of *E*- and *Z*-isomers ($E/Z = 87/13$) in 82% yield. A similar result was obtained even at higher temperature (−15 °C to rt). The use of CH_2Cl_2 as a solvent in this reaction was

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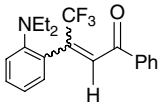
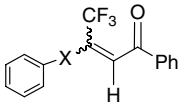
advantageous. From a mechanistic point of view, we propose that trifluoromethyl propargylic carbocation or its equivalent [I] was formed and then reacted with H_2O to give allenol [II], which tautomerized to **2**. Addition of H_2O towards [I] regiospecifically occurred at carbon bearing trifluoromethyl group. A plausible mechanism is shown in Scheme 1.

To trap the intermediate [I], we examined reactions of [I] with carbon nucleophiles under the optimized reaction condition. When **1** was reacted with TMSOTf in CH_2Cl_2[13] at −15 °C, followed by warming to room temperature and then treated with benzene derivatives having activating groups such as anisole, thioanisole and *N*,*N*-diethylaniline at room temperature for several hours, β-trifluoromethylated β-aryl substituted enones **3a–c** were obtained as a mixture of *E*- and *Z*-isomers in 61–96% yields. The *ortho* substituted enone **4a** was obtained in 25% yield in the case of the treatment with *N*,*N*-diethylaniline. Phenol was also reacted with [I] at 0 °C for 1 h to give the corresponding enone **3d** in 93% yield. In contrast, the reaction of [I] with thiophenol or aniline under the same reaction condition afforded β-trifluoromethyl-β-phenylthio or β-trifluoromethyl-β-phenylamino substituted enones **4b**, **4c** in 93% and 14% yields, respectively. However, the reactions of [I] with toluene, benzene, chlorobenzene and trifluoromethylbenzene did not provide the desired products **3g–j** under the same reaction condition, whereas enaminone **2** was obtained as a sole product for every case. This result indicates that intermediate [I] is a quite stable species which does not react with benzene derivatives having deactivating group in the reaction solution. The preparation of **3** was summarized in Table 1.



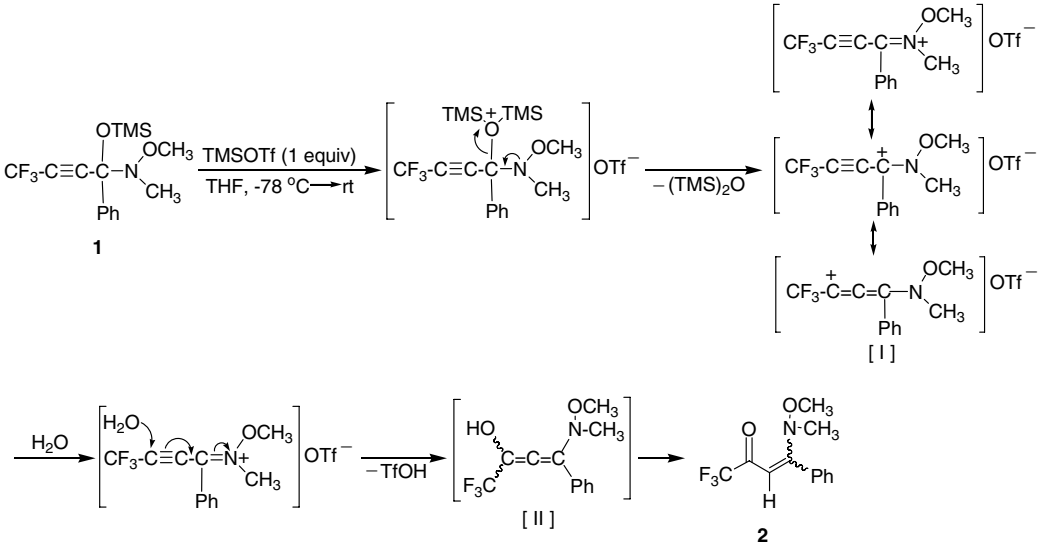
4a



4b (X = S), **4c** (X = NH)

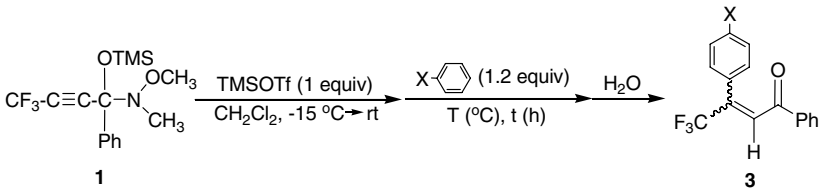
The reaction mechanism could involve the formation of immonium ion intermediate [III] via Friedel–Crafts reaction of [I] with anisole, followed by reaction with trifluoromethanesulfonic acid formed in the reaction process, in which same regiospecificity was also controlled as shown in Scheme 1. Intermediate [III] was further reacted with H_2O to give **3a**. Addition of H_2O towards intermediate [III] led exclusively to allylic hemiaminal intermediate [IV] with perfect regioselectivity, which underwent deamination to afford enone **3a**. A plausible mechanism for the formation of **3a** is shown in Scheme 2.

A similar reaction was extended to allyl trimethylsilane as a silicon-containing π-nucleophile, in which the nucleophile reacted with [I] in an S_E2' fashion to give the corresponding enone **5** in 97% yield. The use of strong nucleophiles, for examples, Grignard reagents such as PhMgBr, MeMgBr and $CH_3C{\equiv}CMgBr$ under the milder reaction condition facilitated the formation of enones **3**. Therefore, treatment of [I] with PhMgBr derivatives at −78 °C for 1 h provided the corresponding enones **3g–j** in 79–85% yields along with regioisomers **6g–j** (less than 6% yield). This reaction could provide a potential method for the preparation of enones, which cannot be prepared via Friedel–Crafts reaction of [I] with benzene derivatives. However, the treatment of [I] with MeMgBr under the same reaction condition resulted in the formation of **3k** and **6k** in 13% and 76% yields, respectively, in which a steric factor seems to play an important role to lead to the formation **6k** instead of the formation of **3k**. Treatment of [I] with $CH_3C{\equiv}CMgBr$ under the same reaction condition resulted in the formation of **3l** and **6l** in 58% and 15% yields, respectively. These trifluoromethylated enones **3**, which methods are limited in the previous literatures,[14–17] are valuable intermediates in synthetic organic chemistry and thus were utilized in recent years to prepare trifluoromethylated indenes[16] and allylic alcohols.[18]



Scheme 1.

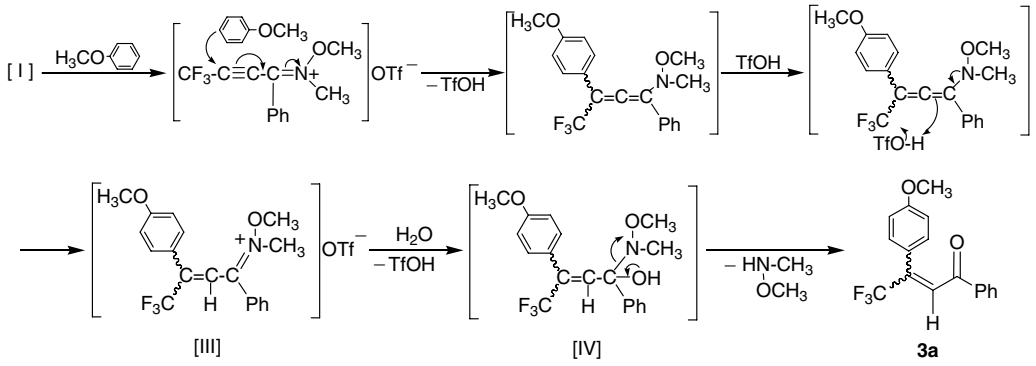
Table 1. Preparation of β-trifluoromethylated β-aryl substituted enones **3**



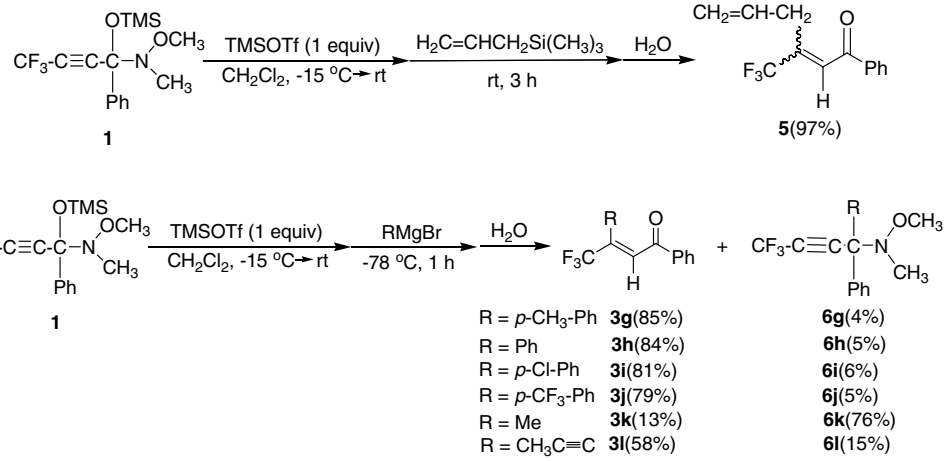
1 **3**

Compound no.	*T* (°C)	*t* (h)	X	Yield[a] (%)	*E*/*Z*[b]
3a	rt	3	CH_3O	96	67/33
3b	rt	5	CH_3S	95	40/60
3c	rt	15	Et_2N	61[c]	75/25
3d	0	1	HO	93	65/35
3e	0	1	HS	—[d]	—
3f	0	1	H_2N	—[d]	—
3g	rt	15	CH_3	—[e]	—
3h	rt	15	H	—[e]	—
3i	rt	15	Cl	—[e]	—
3j	rt	15	CF_3	—[e]	—

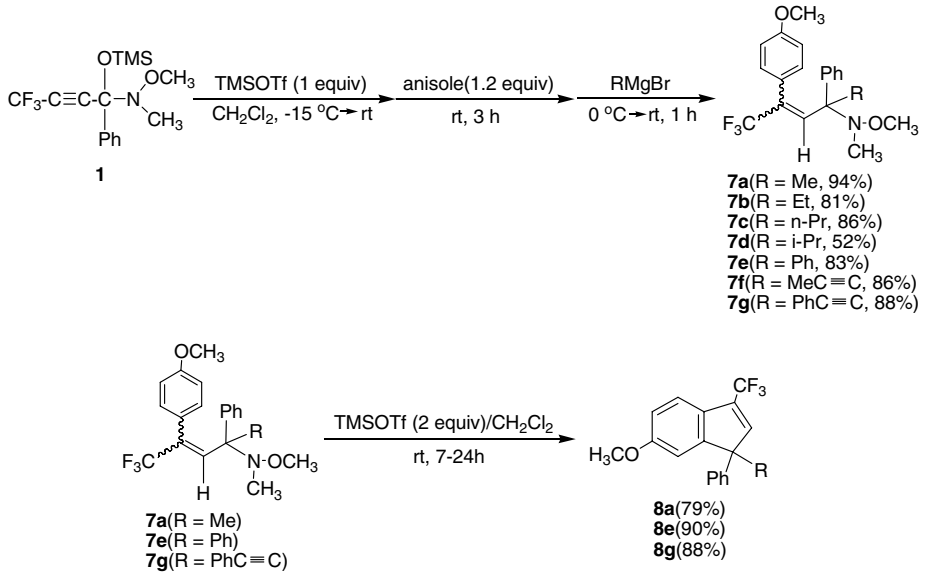
[a] Isolated yield.
[b] *E*/*Z* Ratio was determined by ^{19}F NMR spectroscopy.
[c] *o*-Et_2N–Ph substituted enone **4a** was obtained in 25% yield.
[d] β-Phenylthio and β-phenylamino substituted enones **4b**,**c** were obtained in 93% and 14% yields, respectively.
[e] Enone **2** was obtained in 75–78% yield.



Scheme 2.



Finally, the reaction of intermediate [III] with Grignard reagents was also performed to prepare allylic amine derivatives, which might be extremely valuable synthetic intermediates to give trifluoromethylated indene derivatives via intramolecular cyclization under acidic condition. When [III] was treated with MeMgBr, EtMgBr, *n*-PrMgBr, *i*-PrMgBr, PhMgBr, MeC≡CMgBr and PhC≡CMgBr at 0 °C, followed by stirring at room temperature for 1 h, the corresponding *E*- and *Z*-isomeric mixtures of allylic amine derivatives **7a**–**g** were obtained



in 52–94% yields. The reaction mechanism could be quite similar to the formation of intermediate [IV] as shown in Scheme 2. Cyclization reaction of **7a** by using the use of 2 equiv TMSOTf in CH_2Cl_2 at room temperature for 7 h provided the highest yield of indene compound **8a**.[19] Similarly, indene compounds **8e** and **8g** were obtained in 90% and 88% yields, respectively. Generally, the method for the preparation of trifluoromethylated indenes was quite limited previously and also had a lack of generalization.[20] However, our method provides a generalized and high yield preparation of trifluoromethylated indenes.

Formation of trifluoromethyl propargylic carbocation having methyl group instead of phenyl group at 1-position in compound **1** was not successful and a messy reaction mixture was formed under several reaction conditions.

A typical reaction procedure for the preparation of **7a** is as follows. 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 trifluoromethylated propargyl silyl ether **1** (0.166 g, 0.5 mmol) and methylene chloride (2 mL) and then cooled to −15 °C. TMSOTf (0.111 g, 0.5 mmol) was added at −15 °C, followed by warming to room temperature and then anisole (0.065 g, 0.6 mmol) was added. After stirring at room temperature for 3 h and then cooling to 0 °C, CH_3MgBr (3 M solution in ether, 0.65 mmol) was added. The reaction mixture was stirred at room temperature for 1 h, quenched with saturated NH_4Cl and then extracted with methylene chloride twice. The methylene chloride solution was dried over anhydrous K_2CO_3 and chromatographed on SiO_2 column. Elution with a mixture of hexane and ethyl acetate (9:1) provided 0.172 g of **7a** ($E/Z = 3/1$) in 94% yield. Compound **7a**: Oil: ^{1}H NMR ($CDCl_3$) δ 7.47–7.22 (m, 7H, *Z*-isomer), 7.29–7.21 (m, 5H, *E*-isomer), 7.08 (s, 1H, *E*-isomer), 6.94–6.88 (m, 2H, *Z*-isomer), 6.73 (s, 1H, *Z*-isomer), 6.71–6.66 (m, 4H, *E*-isomer), 3.82 (s, 3H, *Z*-isomer), 3.76 (s, 3H, *E*-isomer), 3.43 (s, 3H, *E*-isomer), 3.36 (s, 3H, *Z*-isomer), 2.35 (s, 3H, *E*-isomer), 2.34 (s, 3H, *Z*-isomer), 1.79 (s, 3H, *Z*-isomer), 1.17 (s, 3H, *E*-isomer); ^{19}F NMR ($CDCl_3$, internal standard $CFCl_3$) δ −57.63 (s, 3F, *Z*-isomer), −67.23 (s, 3F, *E*-isomer); MS, *m*/*z* (relative intensity) 365 (M^+, 1), 305 (100), 227 (84), 197 (69), 177 (24), 118 (12), 91 (12), 77 (13); IR (neat) 3059, 2990, 1609, 1464, 1285, 1172, 1037 cm^{-1}. Anal. Calcd for $C_{20}H_{22}F_3NO_2$: C, 65.74; H, 6.07. Found: C, 65.59; H, 6.00.

Acknowledgement

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19. Spectra data of **8a**: ^{1}H NMR ($CDCl_3$) δ 7.25–6.87 (m, 9H), 3.78 (s, 3H), 1.74 (s, 3H); ^{19}F NMR ($CDCl_3$, internal standard $CFCl_3$) δ −64.59 (s, 3F); MS, *m*/*z* (relative intensity) 304 (M^+, 100), 289 (21), 274 (4), 246 (10), 203 (6), 191 (7), 115 (3); IR (neat) 3064, 2927, 1607, 1464, 1382, 1258, 1128, 697 cm^{-1}. Anal. Calcd for $C_{18}H_{15}F_3O$: C, 71.05; H, 4.97. Found: C, 70.91; H, 4.93.
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