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Synthesis of 4-(Trifluoromethyl)cyclopentenones and 2-(Trifluoromethyl)furans by Reductive Trifluoroacetylation of Ynones

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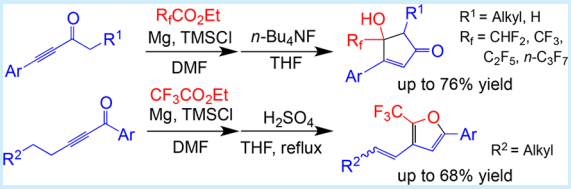
Supporting Information

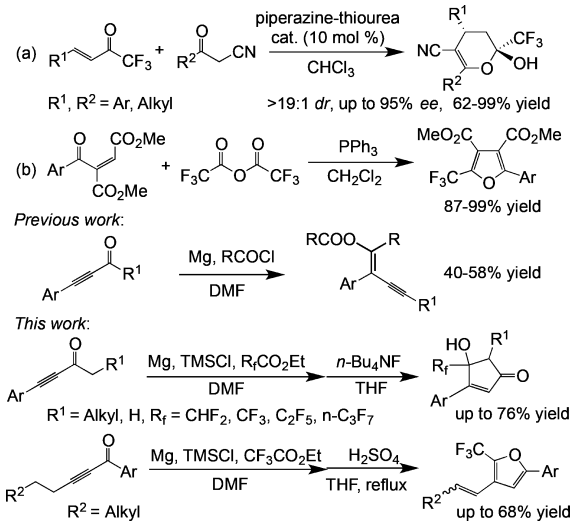
ABSTRACT: Reductive introduction of a fluorine-containing carbon block to readily available conjugated ynones, followed by intramolecular cyclization, successfully gave the corresponding trifluoromethylated cyclopentenones or trifluoromethylated furans in good yields through a simple two-step protocol. The key compound in carbon−carbon bond formation by magnesium-promoted reduction is ethyl trifluoroacetate, which has been rarely used as a fluorine-containing carbon source, especially to electron-deficient carbon atoms in organic synthesis.



The importance of partially fluorinated organic molecules as pharmaceutical drugs, agrochemicals, and organic materials has been enormously enhanced in recent decades.[1] In particular, trifluoromethylated organic molecules are regarded as important chemicals in the field of medicinal science.[2] For example, befloxatone,[3] sitagliptin,[4] and efavirenz[5] are notable drugs containing a trifluoromethyl group with good market performance. Therefore, synthesis of trifluoromethylated organic compounds has been actively pursued in recent years.[6,7] As an example, Zhu and co-workers reported a Michael addition of α-cyanoketones to α,β-unsaturated trifluoromethyl ketones and stereoselective synthesis of α-trifluoromethylated dihydropyrans (Scheme 1, a).[6a] An important milestone for the synthesis of fluorine-containing furan derivatives is the preparation of trifluoromethylated furans through a coupling reaction between enones and trifluoroacetic anhydride as reported by Xu and co-workers in 2011 (Scheme 1, b).[7a] We also disclosed synthetic reactions of partially fluorinated compounds by magnesium-promoted reduction.[8] For instance, trifluoroacetylation of 4-vinylpyridines in the presence of ethyl trifluoroacetate afforded the corresponding β-monotrifluoroacetylated compounds in good yields.[8a]

In our recent work, magnesium-promoted reductive acylation of aromatic ynones in the presence of acyl chlorides afforded the corresponding enyne derivatives,[9] and the triple bond of aromatic ynones was transposed to the neighboring position via the allene intermediate formation and subsequent decomposition in situ (Scheme 1, previous work). In connection with our interest in organofluorine chemistry, we supposed that the use of ethyl trifluoroacetate (**2a**) in reactions with ynone **1** might give a simple β-trifluoroacetylated product, similar to our previous research. In fact, magnesium-promoted reduction of ynones in the presence of chlorotrimethylsilane and ethyl trifluoroacetate **2a** gave acetals of the corresponding β-trifluoroacetylated compounds. However, unlike the aforementioned reactions, the subsequent treatment with tetrabutylammonium fluoride (TBAF) led to the formation of trifluoromethylated cyclopentenones through an aldol-type intramolecular cyclization or treatment with sulfuric acid gave trifluoromethylated furans in good yield (Scheme 1, this work).

Scheme 1. Background of Reductive Synthesis of Trifluoromethylated Cyclopentenones and Trifluoromethylated Furans from Ynones



At first, we chose an aromatic ynone (**1a**) and ethyl trifluoroacetate **2a** as the model substrates to optimize the reaction conditions. The results on the solvent effects and reaction temperature are shown in Table 1. In the study of

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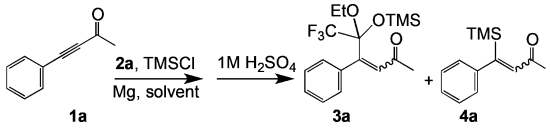
Table 1. Effects of Solvent and Temperature on Mg-Promoted Trifluoroacetylation of Aromatic Ynone 1a[a]



entry	solvent	temp (°C)	GC yield (%) 3a	GC yield (%) 4a
1	NMP	rt	61	19
2	NMP	0	63	10
3	NMP	−10	73	13
4[b]	NMP	−25	65	12
5	DMF	−10	75 (70)[c,d]	20 (10)[c]
6	DMAc	−10	62	25
7	MeCN	−10	no reaction	
8	THF	−10	no reaction	

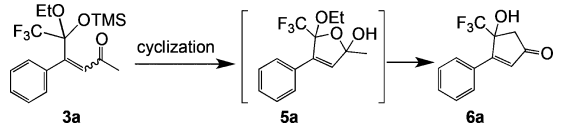
[a]Reaction conditions: **1a** (2 mmol), CF_3CO_2Et **2a** (11 equiv), TMSCl (4 equiv), Mg turnings (3 equiv), solvent (20 mL), N_2 atmosphere, 2−3 h. *n*-Decane was used as the internal standard for GC yields. See Table S1 for reaction optimization. [b]Overnight; a small amount of **1a** was recovered. [c]Isolated yields. [d]*Z*/*E* configuration was determined by NOE measurement, and the ratio (13:1) was determined by GC.

reaction temperature, the reaction at −10 °C was found to be appropriate for this coupling reaction (Table 1, entry 3), while at −25 °C, **1a** was partially recovered although the reaction mixture was stirred overnight (Table 1, entry 4). The *β*-silylated product **4a** was also detected as a byproduct due to the stronger electrophilicity of chlorotrimethylsilane compared to that of **2a**.[10,11] As noted in our previous reports, magnesium-promoted reduction was usually conducted in aprotic polar solvents such as *N*-methyl-2-pyrrolidone (NMP), *N*,*N*-dimethylformamide (DMF), and *N*,*N*-dimethylacetamide (DMAc), and therein, DMF was found to be the most effective solvent, and the desired product, *β*-trifluoroacetylated compound **3a** was obtained in 70% isolated yield with 13:1 *Z*/*E* selectivity (Table 1, entry 5). On the contrary, no reaction occurred in acetonitrile and THF (Table 1, entries 7 and 8).

Subsequently, deacetalization of the product **3a** did not produce the corresponding dicarbonyl compounds as predicted.[12] Instead, intramolecular cyclization reaction occurred to give a dihydrofuran derivative **5a** as an intermediate first and then trifluoromethylated cyclopentenone **6a** as the final product. Treatment of acetal **3a** in trifluoroacetic acid or concentrated sulfuric acid failed to afford a complex mixture (Table 2, entries 1 and 2). In the study on this transformation of **3a**, tetrabutylammonium fluoride in THF was found to be the most appropriate reagent. Notably, intermediate **5a** could be isolated under the conditions of lower reaction temperature and short reaction time (Table 2, entries 3−5), while trifluoromethylated cyclopentenone **6a** was selectively obtained in high yield at room temperature after longer reaction time (Table 2, entries 6−8). The chemical structure of **6a** has been supported by X-ray crystallographic analysis.

Various ynones **1a**−**n** were synthesized, and the results of the coupling reactions under the optimal reaction conditions are shown in Scheme 2. Ynones with monosubstituents at the *α*-position of the carbonyl group gave the desired compounds in moderate yields as a mixture of diastereomers (**6b**−**d**). The efficiency of the reactions was not significantly affected by the electron-donating groups or electron-withdrawing groups on the aromatic rings. The electron-donating group at the *para*-position

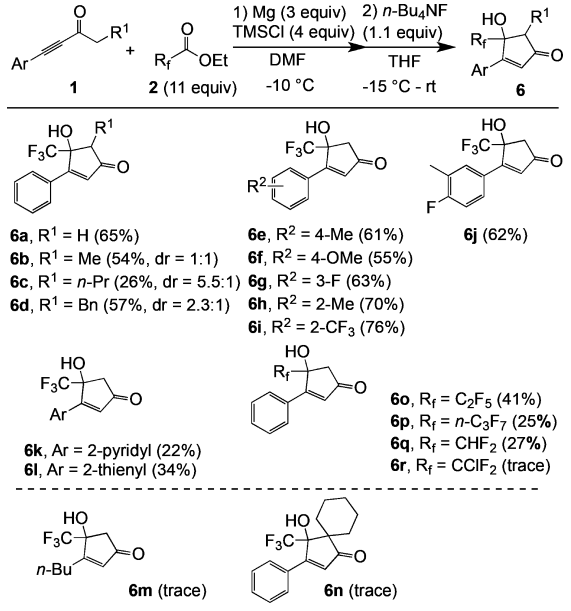
Table 2. Optimization Studies on the Cyclization of Acetal of *β*-Trifluoroacetylated Compound 3a[a]



entry	reagent (equiv)	temp (°C)	time (h)	isolated yield (%) 5a[b]	isolated yield (%) 6a
1	conc H_2SO_4	rt	2	complex mixture	
2	CF_3COOH	rt	24	complex mixture	
3[c]	nBu_4NF (0.5 equiv)	−15	2	94	
4[c]	nBu_4NF (1.1 equiv)	−15	2	97	
5[c]	nBu_4NF (1.5 equiv)	−15	2	75	
6[c]	nBu_4NF (1.3 equiv)	0[d]	5		81
7[c]	nBu_4NF (1.1 equiv)	−15[d]	18		98
8[c]	nBu_4NF (2.0 equiv)	−15[d]	18		94

[a]Reaction conditions: **3a** (1 mmol), N_2 atmosphere. [b]5:1 isomeric mixture of **5a**, determined by ^1H NMR. [c]Solvent: THF (10 mL). [d]Temperature was raised to rt.

Scheme 2. Scope of Structure of Ynones 1 and Fluorine-Containing Acylating Reagents 2



of the phenyl ring slightly decreased the yields (**6e** and **6f**), and that at the *ortho*-position exhibited the increase of yields (**6h**). Substitution by a fluorine atom at *meta*-position afforded **6g** in 63% yield, and a strong electron-withdrawing trifluoromethyl group at the *ortho*-position gave the desired product **6i** in 76% yield.

It is worth noting that two substituents on the aromatic ring were also compatible with this reaction to afford **6j** in 62% yield. Ynones with a heteroaromatic ring also afforded the desired product **6k** and **6l** in 22% and 34% isolated yield, respectively. Interestingly, this reaction could be extended to the introduction of poly- and perfluoroalkyl groups. Under the standard reaction conditions, the reactions using ethyl pentafluoropropionate **2b**, ethyl perfluorobutyrate **2c**, and ethyl difluoroacetate **2d** were compatible to give **6o**, **6p**, and **6q** in 41%, 25%, and 27% yield,

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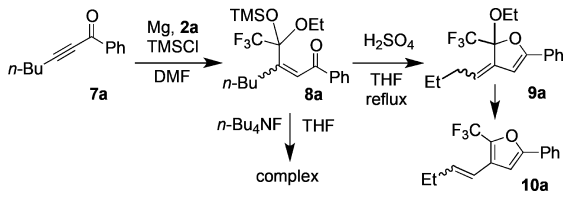
respectively. Nevertheless, ethyl chlorodifluoroacetate **2e** could not be used for the synthesis of fluorine-containing compounds probably due to the reductive substitution reaction of a fluorine or a chlorine atom by chlorotrimethylsilane under the Mg-promoted reduction conditions.[13] On the other hand, it is noteworthy that the stabilizing effect of an aromatic ring played a crucial role in this reaction and only trace amount of desired product (**6m**) was detected with the recovery of most of the starting aliphatic ynone (**1m**), although **1m** (reduction potential: −2.23 V vs Ag/AgCl) had been expected to be reduced under the reaction conditions.[14] As expected, the efficiency of reactions was significantly affected by steric hindrance, to give no desired product (**6n**) when a bulky cyclohexyl group was substituted.

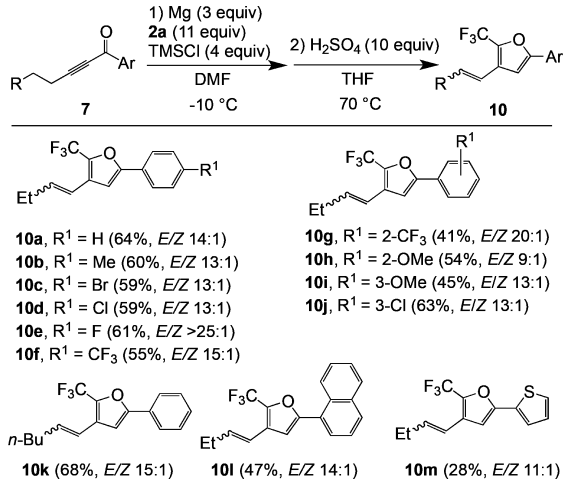
We next concentrated on the trifluoroacetylation of benzoylacetylene derivatives **7** which were readily prepared from alkynes and benzaldehydes. Trifluoroacetylation proceeded smoothly to give **8a** (Z/E = 18:1); however, cyclization of **8a** failed with no formation of cyclopentenone when we directly used tetrabutylammonium fluoride (Scheme 3). After systematic

Scheme 3. Trifluoroacetylation of Benzoylacetylenes 7a



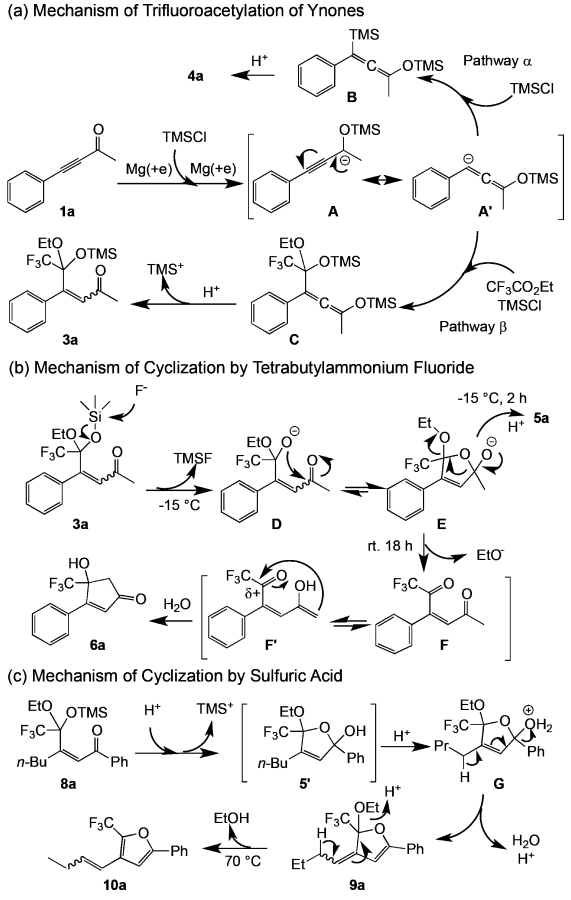
investigation of the cyclization reaction conditions (see Table S2), **8a** could be selectively converted to (*E*)-2-trifluoromethylated furan **10a** with the aid of sulfuric acid in THF under reflux conditions. A variety of trifluoromethylated furans **10** were synthesized, and the results are shown in Scheme 4. Significant

Scheme 4. Scope of Synthesis of 2-Trifluoromethylfurans from Ynones 7



substituent effects could not be observed, and only compounds **7** with an electron-withdrawing group CF_3 or a methoxy group at the *meta*-position gave the desired products in a lower yield (**10f**, **10g**, **10i**). Application of a butyl group instead of an ethyl group to the alkyl group R gave the desired product **10k** in a slightly higher yield. In addition, this synthesis of furan derivatives could be applied to ynones with an aromatic ring such as 1-naphthyl or 2-thienyl group (**10l** and **10m**). On the basis of our previous reports[8b,c,9,10] and investigation on reduction potential[14] of ynones **1**, **7**, chlorotrimethylsilane, and ethyl trifluoroacetate **2a**, plausible reaction mechanisms for the trifluoroacetylation and deacetalization were proposed in Scheme 5. First, a single-

Scheme 5. Proposed Reaction Mechanism



electron transfer from magnesium metal to aromatic ynone **1a** will give an anion radical species, which is attacked by a chlorotrimethylsilane and then obtains the second electron to form an intermediate **A**. Intermediate **A** then undergoes isomerization through the neighboring triple bond, partially leading to the formation of the byproduct, disilylated allene **B** after the second silylation, as shown in pathway α.[10] On the contrary, in pathway β, the ion **A′** attacks ethyl trifluoroacetate followed by the attack of chlorotrimethylsilane to afford an allene **C**.

The allene structure of **C** is a protected form of the carbonyl group and can survive in situ without reduction by magnesium. The subsequent hydrolysis of only silyl enol ether by sulfuric acid gave the acetal of β-trifluoroacetylated compound **3a** (Scheme 5, a). In the mechanism of cyclization, a fluoride ion cleaves the silicon−oxygen bond to give an intermediate **D** at −15 °C. The ion **D** attacks the electron-deficient carbonyl carbon atom to form a dihydrofuran structure **E**. Quench by water at this stage leads to the formation of a compound **5a**. Raising the temperature to room temperature prompted elimination of the ethoxy group from **E** to form 1,4-diketone **F** as an intermediate. The terminal alkene of the enol structure **F′** attacks the electron-deficient carbonyl carbon atom of the trifluoroacetyl group to afford the final compound **6a** (Scheme 5, b).[15] Formation of furan **10a** required strongly acidic conditions under reflux as

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shown in Scheme 5, c. The trimethylsilyl group of **8a** first eliminates after protonation to form a dihydrofuran derivative **5′**. Dehydration from **5′** under the acidic conditions afforded the compound **9a** by way of generation of a stable benzyl cation. Finally, at high temperature, elimination of 1 mol of ethanol from **9a** will give a furan derivative **10a** through the aromatization.

In summary, trifluoroacetylation of aromatic ynones under magnesium-promoted reduction conditions afforded trifluoromethylated cyclopentenones or trifluoromethylated furans in a two-step strategy. Difluoroacetylation and perfluoroacylation could be also achieved under similar reaction conditions. This reaction provides an efficient approach to synthesize cyclopentenones or furans with a trifluoromethyl group in good yields under simple and mild reaction conditions. Further studies on trifluoroacetylation are currently in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03302.

^{1}H, ^{13}C, and ^{19}F NMR spectra of **1j**, **7g**, **3a**, **5a**, **6a−l**,**o−q**, **8a**, **9a**, and **10a−m**; X-ray data for **6a** (PDF)

Accession Codes

CCDC 1489242 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(11) Addition of chlorotrimethylsilane is essential as the reagent for activation of the magnesium surface. An excess amount of ethyl trifluoroacetate is required to avoid silylation; see ref 8 and Table S3.

(12) According to our previous research, alkyl silyl acetals of trifluoromethyl ketones sometimes resist deacetalization; see ref 8.

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(14) To understand the reaction mechanism, the reduction potential of some substrates was measured by cyclic voltammetry; see Table S3 for details. The possibility of the first electron transfer to ethyl trifluoroacetate **2** has been excluded because the reduction potential of **2** was about −2.47 V vs Ag/AgCl in our previous studies.[8a−c]

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