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Synthesis and hetero-Diels–Alder reactions of (*E*)-α-perfluoroalkanesulfonyl-α,β-unsaturated ketones

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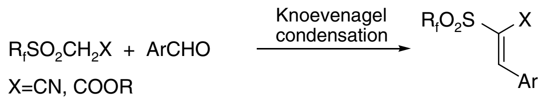
Abstract—Catalyzed by ammonium acetate, the Knoevenagel reactions of β-keto perfluoroalkanesulfones **1** with aromatic aldehydes **2** afforded α-perfluoroalkanesulfonyl-α,β-unsaturated ketones **4** in moderate to good yields. The possible mechanism for the reactions was proposed. These fluorine-containing α,β-unsaturated ketones, which are electron-poor 1-oxa-1,3-butadienes, could be used in inverse electron demand hetero Diels–Alder (HDA) reaction with electron-rich olefins to give tetrasubstituted dihydropyrans **6** in quantitative yields.

The sulfonyl groups are of special interest in organic chemistry for their ambivalent nature.[1–3] They may function either as electrophiles or nucleofugic leaving groups having an electron pair to form sulfinate anions. Moreover, sulfonyl groups can stabilize neighboring carbanions or activate adjacent carbon–carbon multiple bonds for nucleophilic attack and cycloadditions due to their strong electron-withdrawing effect.[4] This capability can be more strengthened by exchanging alkyl or aryl substituents of sulfonyl with stronger electron-withdrawing perfluoroalkyl group R_f.[5,6]

Just for their versatile reactivity, sulfones, called as 'chemical chameleons', are of great importance in organic synthesis.[1–4,7] Among their derivatives, β-keto sulfones have gained wide applications as intermediates in the synthesis of substituted acetylenes, olefins, allenes, vinyl sulfones, polyfunctionalized 4*H*-pyrans and quinolines.[8] Among these studies, however, less attention was focused on the β-keto perfluoroalkanesulfones.

Several groups have reported that the perfluoroalkanesulfonyl acetonitriles and esters $R_fSO_2CH_2X$ (X = CN, COOR), similar to β-keto or β-alkoxycarbonyl aryl sulfones $ArSO_2CH_2COX$ (X = R, OR), undergo Knoevenagel condensation reaction with aromatic aldehydes to give 2-aryl-1-perfluoroalkanesulfonyl acrylonitriles or 3-aryl-2-perfluoroalkanesulfonyl-2-propenoates (Scheme 1).[6,9]

Recently, we found that the reaction of β-keto perfluoroalkanesulfones $R_fSO_2CH_2COR$ ($R_f = ClC_4F_8$, R = Ph (**1a**) or CH_3 (**1b**)) with aldehydes **2** was quite different from that of perfluoroalkanesulfonyl esters under the traditional Knoevenagel condensation conditions, which afforded tetrasubstituted *trans*-2,3-dihydrofurans **3** in good yields.[10] These results could rationally explain that the intermediate α-perfluoroalkanesulfonyl-α,β-unsaturated ketones **4** were a better electrophilic Michael acceptor than α-perfluoroalkanesulfonyl-α,β-unsaturated esters. They then readily underwent Michael addition with another molecule of **1** and were followed by intramolecular nucleophilic displacement to give tetrasubstituted dihydrofuran derivatives (Scheme 2).



Scheme 1.

Keywords: α,β-Unsaturated ketones; Knoevenagel; Ammonium acetate; Hetero Diels–Alder reaction; Dihydropyran.

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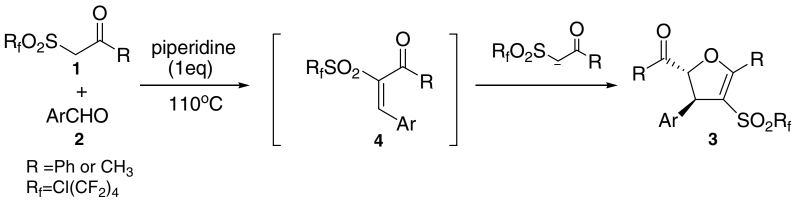


Scheme 2.

Synthesis and utilization of these active α-perfluoroalkanesulfonyl-α,β-unsaturated ketones are nevertheless few mentioned to date.[11] Accordingly, we are interested in their preparation and synthetic applications. As a part of further study on the chemical transformations of β-keto perfluoroalkanesulfones, we now report here the successful stereospecific synthesis of (*E*)-α-perfluoroalkanesulfonyl-α,β-unsaturated ketones **4** by the Knoevenagel condensation reaction between $R_fSO_2CH_2COR$ **1** and aromatic aldehydes **2** with ammonium acetate as catalyst.[12] These fluorine-containing α,β-unsaturated ketones, which are electron-poor 1-oxa-1,3-butadienes, could be used in inverse electron demand hetero Diels–Alder (HDA) reaction with electron-rich olefins to give tetrasubstituted dihydropyrans in quantitative yields.

Initially, various amines (piperidine, DBU, triethylamine) were employed to facilitate the model reaction of **1a** with excessive benzaldehyde **2a** at room temperature for synthesis of the expected α-perfluoroalkanesulfonyl-α,β-unsaturated ketone. Although TLC analysis showed that a small quantity of α,β-unsaturated ketone was formed at the beginning, while it was gradually transformed to dihydrofuran derivative **3a** in the reaction process. This disappointing result could be attributed to the amine's basic property. It snatched a proton from **1a**, and the α,β-unsaturated ketone was readily reacted with the formed anion to give **3a**. To weaken the basicity of the catalyst was, therefore, the key to prevent the undesired Michael addition.

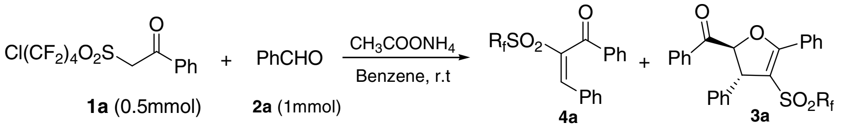
After investigation, it was found that ammonium acetate was a suitable catalyst for the Knoevenagel condensation between **1a** and benzaldehyde **2a** (Table 1). The reaction proceeded smoothly in anhydrous benzene at room temperature, and two products were isolated by column chromatography as white solids (Table 1, entry 1).

On the basis of the spectral data, the byproduct was determined as the dihydrofuran derivative **3a**. For the major product, its MS spectrum presented molecular ion peak at *m*/*z* 506/508. The typical strong infrared absorption of α,β-unsaturated ketone was appeared at $1671\ cm^{-1}$ in IR spectrum. Meanwhile, the ^1H NMR spectrum showed that it existed as one sole isomer. A single peak of the proton linked to newly formed carbon–carbon double bond was at δ 8.12 ppm. The chemical shifts of other 10 aromatic protons were between δ 7.28 and 7.95 ppm. Based on all of the spectral data, this compound was easily identified as the expected condensation product **4a**. The *E*-type configuration of the carbon–carbon double bond was further confirmed by its X-ray single-crystal diffraction analysis (Fig. 1).[13]

Further studies showed that reducing the catalyst loading to 0.2 equiv would decrease the conversion of **1a** and the yield of **4a** (Table 1, entry 2). Addition of molecular sieves could promote the complete transformation of **1a** and improve the yield of **4a** (Table 1, entry 3). Furthermore, several solvents were investigated. Benzene was the best one for this reaction, other solvents, such as CH_3CN and THF, favored the formation of 2,3-dihydrofuran derivative **3a**. Under the established optimized reaction conditions, a series of α-perfluoroalkanesulfonyl-α,β-unsaturated ketones **4** were synthesized from **1** with various aromatic aldehydes **2** in moderate to good yields (Table 2).

As shown in Table 2, cinnamaldehyde and furfural also reacted with **1a** to give the corresponding condensation

Table 1. Knoevenagel reaction between **1a** and **2a** catalyzed by ammonium acetate



Entry	$AcONH_4$ (equiv)	Time (h)	Yield[a] (%)	
			4a	**3a**
1[b]	1	24	74	9
2[b]	0.2	24	67	5
3[c]	1	12	86	5

[a] Isolated yield based on **1a**.

[b] **1a** could not be completely converted. The residual material was not recycled.

[c] 0.2 g molecular sieves (4 Å) was added.

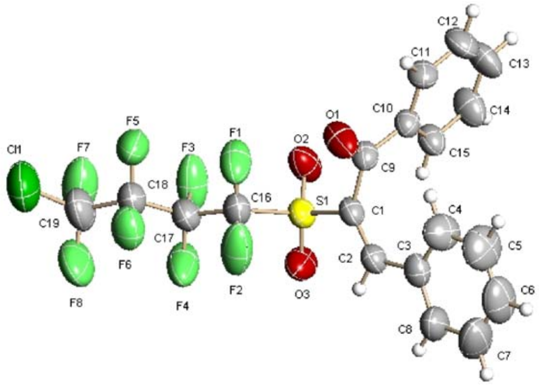
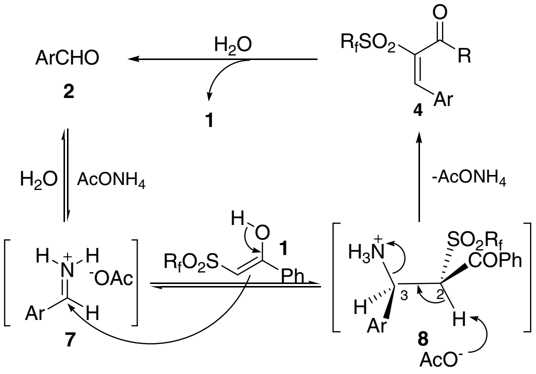


Figure 1. X-ray crystallography of **4a**.



Scheme 3. Proposed mechanisms of the reaction to prepare α-perfluoroalkanesulfonyl-α,β-unsaturated ketones **4**.

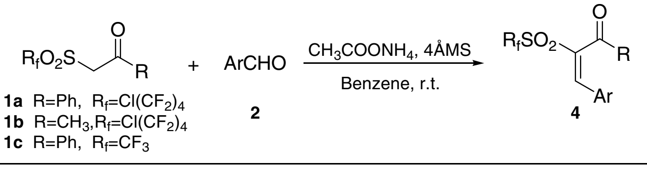
product in good yield under the same conditions (Table 2, entries 6 and 7). However, the reaction of aromatic aldehyde bearing strong electron-attracting group, such as *p*-nitrobenzaldehyde, with **1a** preferably gave 2,3-dihydrofuran derivatives. As for more active **1b**, which always afforded 2,3-dihydrofuran derivatives as major products even reacted with nonactivated aldehyde. While it reacted with furfural to afford the expected product **4h** only in 47% yield, along with tetrasubstituted 2,3-dihydrofuran in 29% yield (Table 2, entry 8). All the products were obtained as (*E*)-isomers, which were fully characterized by their spectral data. Under the same conditions, aliphatic aldehydes reacted with **1** to give complex compounds, which were hard to be separated. Ketones did not react with **1**.

According to the above results, a possible mechanism for the reaction was proposed (Scheme 3). First, the aromatic aldehyde **2** was activated by ammonium acetate to produce the strong electrophile iminium intermediate **7**, which accepted the nucleophilic attack of **1** to afford another intermediate **8**. The two large neighboring groups at C-2 (R_fSO_2) and C-3 (Ar) of **8** preferably adopted trans conformation for the sake of stereohindrance. Finally, the elimination of ammonia stereospecifically gave the expected *E*-type condensation product **4** and regenerated ammonium acetate. As a neutral salt, ammonium acetate could hardly seize the proton of **1** to form the anion, thus holding back the subsequent Michael addition of **1** on α,β-unsaturated ketone **4**. The addition of molecular sieves removed the formed water from the system, which obstructed the hydrolysis of **4** and then insured the complete conversion of **1**.

With α-perfluoroalkanesulfonyl-α,β-unsaturated ketones **4** in hand, we investigated their cycloaddition with diene or 1,3-dipole.[14] To our surprise, **4a** did not react with 1,3-dimethyl-1,3-butadiene or 4-methoxy-benzonitrile-*N*-oxide at all. It could be attributed to the steric hindrance of phenyl group at one-site of **4a**.

Recently, as a powerful method for the preparation of polysubstituted dihydropyrans, the inverse electron demand hetero Diels–Alder (HDA) reaction of oxabutadienes with electron-rich olefins has attracted great attentions.[15] The cycloadduct dihydropyrans, and their

Table 2. Knoevenagel condensation reaction between **1** and aromatic aldehydes **2** catalyzed by ammonium acetate



Entry	**1**	Ar in **2**	Time (h)	Product	Yield[a] (%)
1	**1a**	C_6H_5 (**2a**)	12	**4a**	86
2	**1a**	*p*-$CH_3OC_6H_4$ (**2b**)	12	**4b**	71
3	**1a**	*p*-$CH_3C_6H_4$ (**2c**)	12	**4c**	83
4	**1a**	*p*-BrC_6H_4 (**2d**)	16	**4d**	63[b]
5	**1a**	*o*-BrC_6H_4 (**2e**)	16	**4e**	51
6	**1a**	$C_6H_5CH{=}CH$ (**2f**)	4	**4f**	78
7	**1a**	2-furyl (**2g**)	8	**4g**	94
8	**1b**	2-furyl (**2g**)	8	**4h**	47[c]
9	**1c**	C_6H_5 (**2a**)	12	**4i**	90
10	**1c**	*p*-BrC_6H_4 (**2d**)	16	**4j**	54

[a] Isolated yield based on **1**.

[b] This product could not be isolated from the excessive *p*-bromobenzaldehyde.

[c] Tetrasubstituted 2,3-dihydrofuran was also isolated in 29% yield.

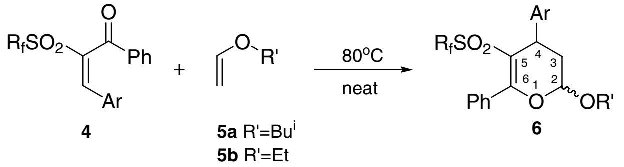
derived tetrahydropyrans, are prevalent structural subunits in numerous important natural products.[16] Due to the strong electron-withdrawing ability of perfluoroalkanesulfonyl groups, α-perfluoroalkanesulfonyl-α,β-unsaturated ketones **4** may act as one sort of electron-poor 1-oxa-1,3-butadienes to react with electron-rich olefins.

We first tried the HDA reaction of **4g** with excessive *iso*-butyl vinyl ether **5a**. To our delight, the cycloaddition proceeded smoothly under solvent-free condition at 80 °C. The reaction was completed within 3 h, and the product **6e** was formed in nearly quantitative yield with a mixture of cis- and trans-diastereomers in a ratio of 66:34 (Table 3, entry 5). The dihydropyran structure was unambiguously established by related spectral data, including IR, MS, ^{1}H, and ^{13}C NMR. The relative configuration of each isomer could be ascertained through ^{1}H–^{1}H NOESY experiment, as well as comparing the coupling constant of the anomeric proton H-2 signal in its ^{1}H NMR. Consulting the studies of Collignon et al.[15e] and Tietze et al.,[15g] the observation of an NOE effect between the anomeric proton H-2 and the *ortho*-proton H-5′ of furan-2-yl or the relative greater coupling constant of H-2 in minor component indicated its 2,4-trans configuration; for the major component, the absence of NOE effect or the smaller coupling constant of the anomeric proton H-2 confirmed its 2,4-cis-configuration.

It was found that lowering the temperature or adding other solvents would dramatically slow down the reaction and suppress the conversion of **4g**. Under the established conditions (80 °C, solvent-free), other α-perfluoroalkanesulfonyl-α,β-unsaturated ketones **4** also reacted smoothly with vinyl ether to give the corresponding dihydropyran derivatives **6** in quantitative yields (Table 3).

All the products were diastereomeric mixtures. Some of them could be separated by column chromatography. The trans- or cis-configuration of each diastereomer was established by comparing coupling constants of two isomers' anomeric protons. The relative configurations of the isomers of **6c** and **6e** were also confirmed by ^{1}H–^{1}H NOESY experiments.

Table 3. HDA reaction of **4** with vinyl ether **5**



Entry	4	5	Time (h)	Product	Yield[a] (%)	cis:trans[b]
1	**4a**	**5a**	5	**6a**	98	58:42
2	**4b**	**5a**	5	**6b**	99	66:34[c]
3	**4c**	**5b**	5	**6c**	97	53:47[c]
4	**4f**	**5a**	3	**6d**	96	54:46
5	**4g**	**5a**	3	**6e**	96	66:34
6	**4g**	**5b**	3	**6f**	97	64:36
7	**4i**	**5b**	4	**6g**	97	53:47

[a] Isolated yield based on **4**.

[b] Determined by ^{1}H NMR.

[c] The trans- and cis-diastereomeric mixtures could not be separated.

In summary, we have established the stereospecific synthesis of (*E*)-3-aryl-2-perfluoroalkanesulfonyl-1-phenylprop-2-en-1-one from the condensation reaction between β-keto perfluoroalkanesulfones and aromatic aldehydes in the presence of ammonium acetate. These electron-poor α-perfluoroalkanesulfonyl-α,β-unsaturated ketones readily reacted with electron-rich olefins such as vinyl ethers to afford the tetrasubstituted 3,4-dihydro-2*H*-pyran derivatives in quantitative yields. Further studies on the diastereoselective and enantioselective tandem-sequence Knoevenagel–hetero-Diels–Alder reaction of β-keto perfluoroalkanesulfones, aldehydes, and electron-rich olefins are in progress.

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13. Crystal data for compound **4a** (CCDC No.: CCDC 293269): $C_{19}H_{11}F_8O_3ClS$, $M_W = 506.79$; monoclinic, $P2[1]/n$; $a = 12.281\ (10)$ Å, $b = 8.305(7)$ Å, $c = 20.906(17)$ Å; $\alpha = 90°$, $\beta = 100.13(10)°$, $\gamma = 90°$; $V = 2099.2(3)$ Å^3; $T = 293(2)$ K; $Z = 4$, $D_c = 1.604$ Mg m^{-3}; μ (Mo Kα) = 0.371 mm^{-1}; $\theta/2\theta$ scan mode 1.80°–26.00°; F(000) = 1016; reflections collected/unique: 11091/4129 ($R_{int} = 0.0546$); $I > 2\sigma(I) = 2801$; parameter = 289; goodness of fit: 1.075; final R indices $[I > 2\sigma(I)]$, $R_1 = 0.0827$, $wR_2 = 0.2568$; R indices (all data), $R_1 = 0.1042$, $wR_2 = 0.2826$.
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