REACTIONS OF 1-SUBSTITUTED 2,2-DIFLUOROSTYRENES WITH DIANIONS OF 1,3-DIKETONES: NOVEL SYNTHESIS OF 4H-PYRAN-4-ONE DERIVATIVES

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Abstract - Treatment of 1-substituted 2,2-difluorostyrenes with dianions of 1,3-diketones, which are generated via the reaction of 1,3-diketones with 4 equiv. of LDA in THF at -78 °C, resulted in the formation of 4H-pyran-4-one derivatives in moderated yields by warming to 25 °C.

Due to the unique reactivity of gem-difluoroolefins toward nucleophiles, gem-difluoroolefins can be used as a useful synthetic intermediate for the preparation of fluorinated or nonfluorinated compounds.1 Although many efforts have been made for the investigation of nucleophilic reaction of gem-difluoroolefins,2–4 only limited work has been directed to the synthetic application of gem-difluoroolefins,5 especially for the formation of heterocyclic compounds. For example, the reaction of gem-difluorinated ketene dithioacetals with only a bidendate sulfur nucleophile afforded heterocyclic ketene thioacetals via successive replacement of the two fluorines.5a Recently, we have also reported an efficient method for the synthesis of 2,2-difluoro-1-phenylthiostyrene(1a) from 2,2,2-trifluoro-1,1-bis(phenylthio)ethylbenzene6 and the synthetic application of this compound for the preparation of various types of heterocyclic ketene acetals via exocyclization of gem-difluoroolefins with bidendate heteroatom nucleophiles.7 This unique reactivity of 2,2-difluoro-1-phenylthiostyrene(1a) toward bidendate heteroatom nucleophiles prompted us to investigate the reaction of various types of 1-substituted 2,2-difluorostyrenes(1) including 2,2-difluoro-1-
phenylthiotyrene (1a) with dianion of 1,3-diketones (2) as a carbon nucleophile. In this communication, we wish to report a preliminary result of this reaction. When the reaction of 2,2-difluoro-1-phenylthiostyrene (1a) with dianion of 2,4-pentanedione (2a) generated by the treatment of 2,4-pentanedione with 4 equiv. of LDA was performed at -78 °C, monosubstituted product (3a) (E : Z = 78 : 22) and 2,6-disubstituted 4H-pyran-4-one derivative (4a) were obtained in 63 % and 11 % isolated yields, respectively. The use of 2 or 3 equiv. of LDA to generate a dianion of 2a did not complete this reaction, while the starting material was always recovered. Assignment of isomers 3a was based on the chemical shifts for vinyl fluorine in $^{19}$F nmr and allylic protons in $^1$H nmr. Generally, allylic protons which are arranged to phenylthio group (E-isomer) are more deshielded than those of Z-isomer.

The high yield formation of 4a was accomplished by the reaction of 1a with dianion of 2a at -78 °C, followed by warming to room temperature. Under this reaction condition, 4a was isolated in 65 % yield, while 3a was not observed at all. This result indicates that 4a might be formed via the exocyclization of enolate ion of 3a. One experimental method for probing the formation of 4a via exocyclization of enolate ion of 3a is the reaction of isolated 3a with base. In order to confirm this indication, 3a was treated with sodium hydride (1.2 equiv.) in THF at room temperature. The adduct (4a) was formed in 85 % isolated yield, which supported the proposed pathway. Therefore, the plausible mechanism for the formation of 4a can be proposed as shown in Figure 1. Initial attack of more nucleophilic carbon in dianion [I] on the starting material (1a) resulted in the formation of intermediate [II] via addition and β-defluorination reaction. Exocyclization via oxygen nucleophilic attacks on fluorovinyl carbon in intermediate [II], followed by β-defluorination initially provided intermediate [III] which gives the final adduct (4a) via 1,3-proton shift.
Similarly, the reactions of 1a with dianions of 3-methyl-2,4-pentanedione(2b), 3-ethyl-2,4-pentanedione(2c), and 1-phenyl-1,3-butanedione(2d) afforded the corresponding 4H-pyran-4-one derivatives (4b)(58 %), (4c)(64 %), and (4d)(67 %), respectively. In order to examine the reactivity of 2,2-difluorostyrenes substituted by hydrogen, methyl, phenyl, and trifluoromethyl group instead of phenylthio group at C-1 position, we performed the reactions of those 2,2-difluorostyrenes(1b-e) with dianion of 2a under the same reaction conditions. When 2,2-difluorostyrene(1b) was treated with dianion of 2a at -78 °C, followed by warming to room temperature, the corresponding 4H-pyran-4-one derivative (4e) was obtained in 21 % isolated yield. The reactions of 2,2-difluoro-1-methylstyrene(1c) and 2,2-difluoro-1-phenylstyrene(1d) with dianion of 2a under the same reaction conditions gave the corresponding 4H-pyran-4-one derivatives (4f) and (4g) in 26 % and 48 % isolated yields, respectively.
The monosubstituted vinyl fluoride derivatives similar to 3a were not detected under the employed reaction conditions. All results are summarized in Table 1.

Table 1. Preparation of 4H-Pyran-4-one Derivatives (4)

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>CH₃</td>
<td>H</td>
<td>SC₆H₅</td>
<td>65</td>
</tr>
<tr>
<td>4b</td>
<td>CH₃</td>
<td>CH₃</td>
<td>SC₆H₅</td>
<td>58</td>
</tr>
<tr>
<td>4c</td>
<td>CH₃</td>
<td>C₂H₅</td>
<td>SC₆H₅</td>
<td>64</td>
</tr>
<tr>
<td>4d</td>
<td>C₆H₅</td>
<td>H</td>
<td>SC₆H₅</td>
<td>67</td>
</tr>
<tr>
<td>4e</td>
<td>CH₃</td>
<td>H</td>
<td>H</td>
<td>21</td>
</tr>
<tr>
<td>4f</td>
<td>CH₃</td>
<td>H</td>
<td>CH₃</td>
<td>26</td>
</tr>
<tr>
<td>4g</td>
<td>CH₃</td>
<td>H</td>
<td>C₆H₅</td>
<td>48</td>
</tr>
</tbody>
</table>

However, treatment of 2,2-difluoro-1-trifluoromethylstyrene (1e) with dianion of 2a at -78 °C, followed by warming to room temperature resulted in formation of unexpected 4H-pyran-4-one derivative (4h) in 42 % isolated yield. The formation of 4h can be rationalized by the further exocyclization of 4H-pyran-4-one derivative (4i), generated via dehydrofluorination of the corresponding 4H-pyran-4-one derivative having trifluoromethyl group, with dianion of 2a. Further study for the preparation of 4H-pyran-4-one derivative (4h) and synthetic utility of this reaction are now in progress.
EXPERIMENTAL

Melting points were measured with a Tomas Hoover capillary melting points apparatus and are uncorrected.
Ir spectra were recorded with a Shimadzu IR-435 spectrophotometer. $^1$H-Nmr spectra were taken by JEOL PMX60Si and Varian Gemini 200 with Si(CH$_3$)$_4$ as an internal standard. $^{19}$F-Nmr spectra were taken by Brucker Ac-100F with CFCl$_3$ as an internal standard. Mass spectra (Ms) and high resolution mass spectra (HRms) were recorded on a JEOL JMS-DX303 spectrometer (EI). Silica gel (230 - 400 mesh, Merck Art 9385) was used for flash column chromatography.

(E)- and (Z)-6-Fluoro-7-phenyl-7-phenylthio-hept-6-ene-2,4-dione (3a)

To a THF (10 ml) solution of 2,4-pentanedione (0.100 g, 1.0 mmol) was added LDA (4.0 mmol) at -78 °C, and the reaction mixture was stirred at -78 °C for 30 min under argon atmosphere. 2,2-Difluoro-1-phenylthiostyrene (0.248 g, 1.0 mmol) was added by dropwise at -78 °C and the reaction mixture was stirred at -78 °C for 2 h. The reaction mixture was poured on ice water and extracted with ethyl acetate. The ethyl acetate solution was dried over anhydrous MgSO$_4$ and chromatographed on SiO$_2$ column. Elution with a mixture of hexane and ethyl acetate (2 : 1) provided (E)- and (Z)-6-fluoro-7-phenyl-7-phenylthio-hept-6-ene-2,4-dione (3a) (0.207 g, 63 %).

3a (E): mp 53 - 54 °C; $^1$H nmr (CDCl$_3$) δ 7.33 - 7.05 (m, 11H), 5.58 (s, 1H), 3.90 (d, $J = 22.0$ Hz, 2H), 2.05 (s, 3H); $^{19}$F nmr (CDCl$_3$) δ -87.0 (t, $J = 22.0$ Hz, 1F); ms, m/z 328 (M$^+$, 51), 270 (97), 245 (26), 244 (100), 223 (31), 219 (16), 165 (82), 85 (100), 45 (45); HR-mrs calcd for C$_{19}$H$_7$O$_2$FS: 328.4053, found 328.0935; ir (KBr) 3071, 3018.2950, 1654, 1536, 1405, 1316, 1233, 1028, 743, 692 cm$^{-1}$. Anal. Calcd for C$_{19}$H$_7$O$_2$FS: C, 69.49; H, 5.22. Found: C, 69.64; H, 5.17.

3a (Z): oil; $^1$H nmr (CDCl$_3$) δ 7.32 - 7.09 (m, 11H), 5.57 (s, 1H), 3.35 (d, $J = 22.0$ Hz, 2H), 2.09 (s, 3H); $^{19}$F nmr (CDCl$_3$) δ -88.5 (t, $J = 22.0$ Hz, 1F). 2-Methyl-6-(1-phenylthiobenzyl)-4H-pyran-4-one (4a) (0.034 g, 11 %) was obtained as a minor product.

2-Methyl-6-(1-phenylthiobenzyl)-4H-pyran-4-one (4a)

To a THF (10 ml) solution of 2,4-pentanedione (0.100 g, 1.0 mmol) was added LDA (4.0 mmol) at -78 °C, and the reaction mixture was stirred at -78 °C for 30 min under argon atmosphere. 1-Phenylthio-2,2-difluorostyrene (0.248 g, 1.0 mmol) was added by dropwise at -78 °C and the reaction mixture was stirred at -78 °C for 2 h, followed by warming to room temperature for 5 h. The reaction mixture was poured on ice water and extracted with ethyl acetate. The ethyl acetate solution was dried over anhydrous
MgSO₄ and chromatographed on SiO₂ column. Elution with a mixture of hexane and ethyl acetate (2 : 1) provided 2-methyl-6-(1-phenylthiobenzyl)-4H-pyran-4-one (4a) (0.200 g, 65 %). 4a : oil; ¹H nmr (CDCl₃) δ 7.56 - 7.22 (m, 10H), 6.29 (d, J = 2.2 Hz, 1H), 6.01 (d, J = 2.2 Hz, 1H), 5.06 (s, 1H), 2.18 (s, 3H); ms, m/z 308 (M⁺, 100), 223 (29), 205 (62), 200 (100), 147 (28), 128 (62), 115 (45), 109 (48), 105 (56), 85 (23); HR-ms calcd for C₁₅H₁₆O₂S 308.3994, found 308.0863; ir (neat) 3100, 1660, 1630, 1490, 1440, 1400, 930, 880, 750, 700 cm⁻¹. Anal. Calcd for C₁₅H₁₆O₂S: C, 74.00; H, 5.23. Found: C, 73.79; H, 5.28.

2,3-Dimethyl-6-(1-phenylthiobenzyl)-4H-pyran-4-one (4b)
The same procedure as above (synthesis of 4a) using 3-methyl-2,4-pentanedione instead of 2,4-pentanedione provided 2,3-dimethyl-6-(1-phenylthiobenzyl)-4H-pyran-4-one (4b) (58 %). 4b : oil; ¹H nmr (CDCl₃) δ 7.49 - 7.21 (m, 10H), 6.33 (s, 1H), 5.07 (s, 1H), 2.20 (s, 3H), 1.89 (s, 3H); ms, m/z 322 (M⁺, 29), 213 (100), 185 (33), 109 (42); HR-ms calcd for C₂₀H₁₈O₂S 322.4262, found 322.1041; ir (neat) 3090, 1660, 1620, 1420, 1390, 1160, 940, 740, 700 cm⁻¹. Anal. Calcd for C₂₀H₁₈O₂S: C, 74.50; H, 5.63. Found: C, 74.33; H, 5.71.

3-Ethyl-2-methyl-6-(1-phenylthiobenzyl)-4H-pyran-4-one (4c)
The same procedure as above (synthesis of 4a) using 3-ethyl-2,4-pentanedione instead of 2,4-pentanedione provided 3-ethyl-2-methyl-6-(1-phenylthiobenzyl)-4H-pyran-4-one (4c) (64 %). 4c : oil; ¹H nmr (CDCl₃) δ 7.47 - 7.20 (m, 10H), 6.31 (s, 1H), 5.06 (s, 1H), 2.38 (q, J = 7.0 Hz, 2H), 2.20 (s, 3H), 1.01 (t, J = 7.0 Hz, 3H); ms, m/z 336 (M⁺, 6), 227 (100), 199 (13), 109 (3); HR-ms calcd for C₂₁H₂₀O₂S 336.4530, found 336.1191; ir (neat) 2950, 1650, 1610, 1400, 1150, 920, 730, 680 cm⁻¹. Anal. Calcd for C₂₁H₂₀O₂S: C, 74.97; H, 5.99. Found: C, 74.75; H, 6.07.

2-Phenyl-6-(1-phenylthiobenzyl)-4H-pyran-4-one (4d)
The same procedure as above (synthesis of 4a) using 1-phenyl-1,3-butanedione instead of 2,4-pentanedione provided 2-phenyl-6-(1-phenylthiobenzyl)-4H-pyran-4-one (4d) (67 %). 4d : oil; ¹H nmr (CDCl₃) δ 7.75 - 7.65 (m, 2H), 7.55 - 7.25 (m, 13H), 6.60 (d, J = 2.1 Hz, 1H), 6.29 (d, J = 2.1 Hz, 1H), 5.18 (s, 1H); ms, m/z 370 (M⁺, 95), 262 (100), 233 (100), 204 (17), 131 (15), 115 (10), 109 (29); HR-ms calcd for C₂₄H₁₆O₂S 370.4702, found 370.1046; ir (neat) 3000, 1640, 1600, 1430, 1380, 1010, 930, 750, 680
cm$^{-1}$. Anal. Calcd for C$_{24}$H$_{18}$O$_2$S: C, 77.81; H, 4.90. Found: C, 77.99; H, 4.84.

2-Benzyl-6-methyl-4$H$-pyran-4-one (4e)

The same procedure as above (synthesis of 4a) using 2,2-difluorostyrene instead of 2,2-difluoro-1-phenylthiostyrene provided 2-benzyl-6-methyl-4$H$-pyran-4-one (4e) (21%). 4e: oil; $^1$H nmr (CDCl$_3$) $\delta$ 7.32 - 7.18 (m, 5H), 6.01 (d, J = 2.1 Hz, 1H), 5.99 (d, J = 2.1 Hz, 1H), 3.75 (s, 2H), 2.19 (s, 3H); ms, m/z 200 (M$^+$, 68), 171 (14), 157 (21), 128 (31), 115 (100), 95 (20), 91 (44), 85 (39), 65 (45), 63 (22), 51 (37), 43 (55); HR-ms calcd for C$_{15}$H$_{12}$O$_2$ 200.2358, found 200.0851; ir (neat) 2950, 1650, 1600, 1380, 1020, 920, 750, 680 cm$^{-1}$. Anal. Calcd for C$_{15}$H$_{12}$O$_2$: C, 77.98; H, 6.04. Found: C, 77.73; H, 6.09.

2-Methyl-6-(1-methylbenzyl)-4$H$-pyran-4-one (4f)

The same procedure as above (synthesis of 4a) using 2,2-difluoro-1-methylstyrene instead of 2,2-difluoro-1-phenylthiostyrene provided 2-methyl-6-(1-methylbenzyl)-4$H$-pyran-4-one (4f) (26%). 4f: oil; $^1$H nmr (CDCl$_3$) $\delta$ 7.42 - 7.25 (m, 5H), 6.17 (d, J = 2.1 Hz, 1H), 6.07 (d, J = 2.1 Hz, 1H), 3.93 (q, J = 7.0 Hz, 1H), 2.24 (s, 3H), 1.62 (d, J = 7.0 Hz, 3H); ms, m/z 214 (M$^+$, 37), 199 (44), 171 (100), 130 (51), 129 (44), 115 (36), 105 (28), 103 (25), 77 (33), 69 (27); HR-ms calcd for C$_{14}$H$_{14}$O$_2$ 214.2626, found 214.1010; ir (neat) 2950, 1640, 1600, 1380, 1020, 920, 750, 680 cm$^{-1}$. Anal. Calcd for C$_{14}$H$_{14}$O$_2$: C, 78.48; H, 6.59. Found: C, 78.31; H, 6.52.

2-Methyl-6-(1-phenylbenzyl)-4$H$-pyran-4-one (4g)

The same procedure as above (synthesis of 4a) using 2,2-difluoro-1-phenylstyrene instead of 2,2-difluoro-1-phenylthiostyrene provided 2-methyl-6-(1-phenylbenzyl)-4$H$-pyran-4-one (4g) (48%). 4g: oil; $^1$H nmr (CDCl$_3$) $\delta$ 7.38 - 7.10 (m, 10H), 6.08 (d, J = 2.1 Hz, 1H), 5.95 (d, J = 2.1 Hz, 1H), 5.21 (s, 1H), 2.17 (s, 3H); ms, m/z 276 (M$^+$, 67), 258 (14), 233 (28), 215 (22), 192 (100), 171 (15), 167 (45), 105 (22), 43 (16); HR-ms calcd for C$_{19}$H$_{16}$O$_2$ 276.3334, found 276.1140; ir (neat) 2950, 1640, 1600, 1480, 1380, 1020, 920, 850, 730, 680 cm$^{-1}$. Anal. Calcd for C$_{19}$H$_{16}$O$_2$: C, 82.59; H, 5.84. Found: C, 82.68; H, 5.76.

$\alpha,\alpha$-Bis(6-methyl-4$H$-pyran-4-one-2-yl)toluene (4h)
The same procedure as above (synthesis of 4a) using 2,2-difluoro-1-trimethylstyrene instead of 2,2-difluoro-1-phenylthiostyrene provided \( \alpha,\alpha \)-bis(6-methyl-4H-pyran-4-one-2-yl)toluene (4h) (42\%).  

4h: mp 95 - 96 °C; \( ^1H \) nmr (CDCl\(_3\)) \( \delta \) 7.42 - 7.20 (m, 5H), 6.10 (d, \( J = 2.2 \) Hz, 2H), 6.07 (d, \( J = 2.2 \) Hz, 2H), 4.95 (s, 1H), 2.22 (s, 6H); ms, m/z 308 (M\(^+\), 82), 237 (20), 224 (36), 200 (61), 171 (78), 153 (27), 152 (29), 139 (30), 85 (51), 69 (100), 45 (76); HR-ms calcd for C\(_{19}\)H\(_{16}\)O\(_4\) 308.3330, found 308.1041; ir(KBr) 3090, 1670, 1625, 1400, 1150, 930, 870, 740, 710 cm\(^{-1}\). Anal. Calcd for C\(_{19}\)H\(_{16}\)O\(_4\): C, 74.01; H, 5.23. Found: C, 74.21; H, 5.10.

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REFERENCES


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