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

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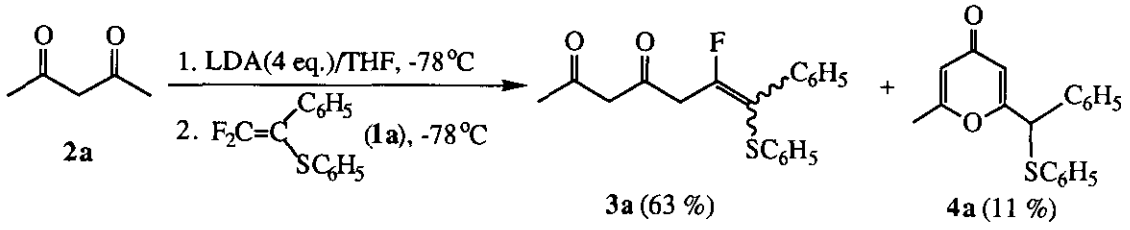
**Abstract** - Treatment of 1-substituted 2,2-difluorostyrenes with dianions of 1,3-diketones, which are generated *via* the reaction of 1,3-diketones with 4 equiv. of LDA in THF at -78 °C, resulted in the formation of 4*H*-pyran-4-one derivatives in moderated yields by warming to 25 °C.

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)ethylbenzene[6] 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 4*H*-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.

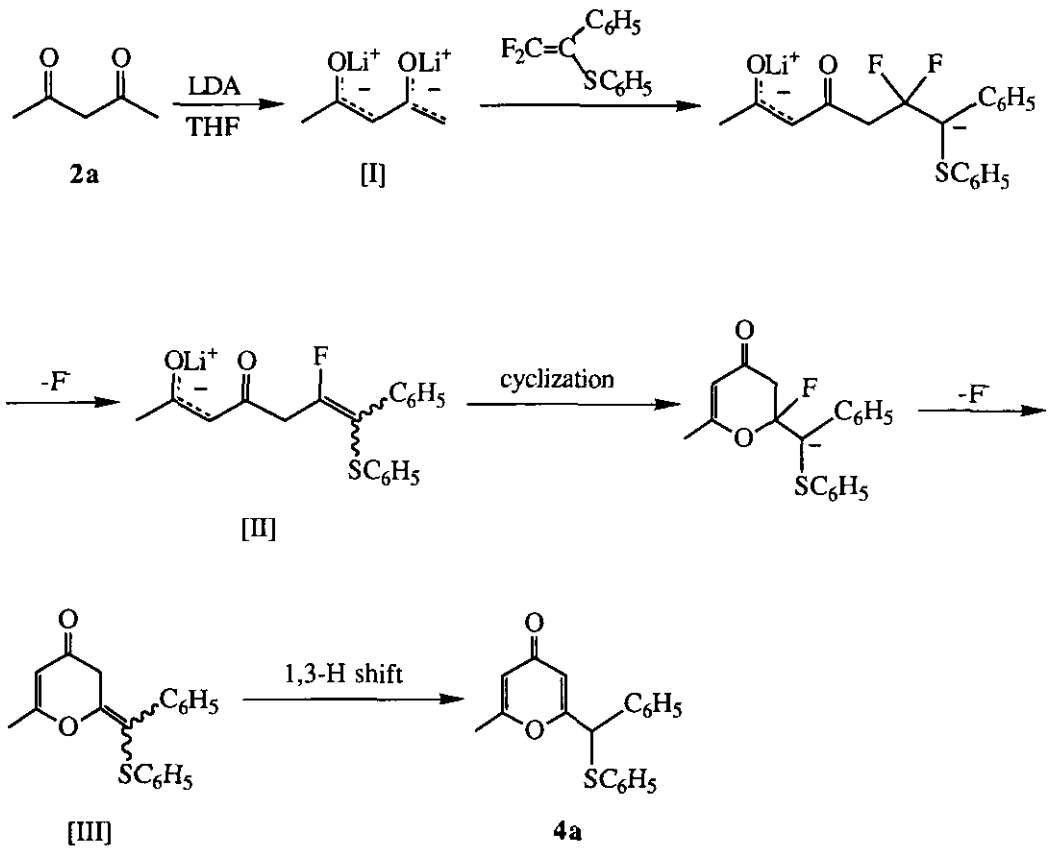
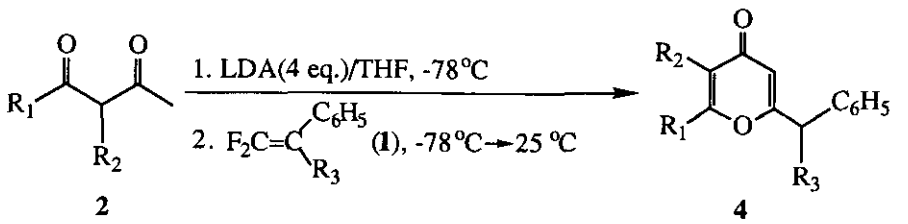



Figure 1. The plausible mechanism for the formation of **4a**

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 4*H*-pyran-4-one derivatives (**4b**)(58 %), (**4c**)(64 %), and (**4d**)(67 %), respectively. In order to examine the reactivity of 2,2-difluorostyrenes[8] 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 4*H*-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 4*H*-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.

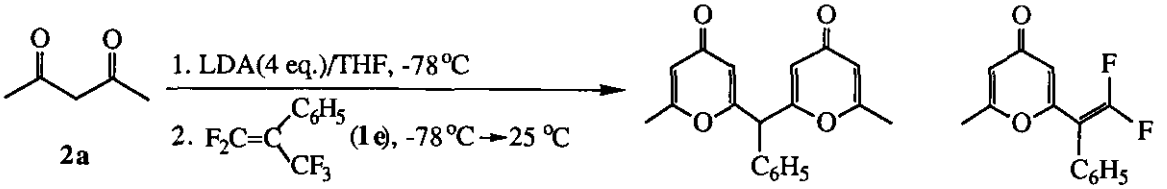
Table 1. Preparation of 4*H*-Pyran-4-one Derivatives (**4**)




**2** **4**

| Compound No. | $R_1$ | $R_2$ | $R_3$ | Yield(%) |
|---|---|---|---|---|
| **4a** | $CH_3$ | H | $SC_6H_5$ | 65 |
| **4b** | $CH_3$ | $CH_3$ | $SC_6H_5$ | 58 |
| **4c** | $CH_3$ | $C_2H_5$ | $SC_6H_5$ | 64 |
| **4d** | $C_6H_5$ | H | $SC_6H_5$ | 67 |
| **4e** | $CH_3$ | H | H | 21 |
| **4f** | $CH_3$ | H | $CH_3$ | 26 |
| **4g** | $CH_3$ | H | $C_6H_5$ | 48 |

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 4*H*-pyran-4-one derivative (**4h**) in 42 % isolated yield. The formation of **4h** can be rationalized by the further exocyclization of 4*H*-pyran-4-one derivative (**4i**), generated *via* dehydrofluorination of the corresponding 4*H*-pyran-4-one derivative having trifluoromethyl group, with dianion of **2a**. Further study for the preparation of 4*H*-pyran-4-one derivative (**4h**) and synthetic utility of this reaction are now in progress.




**2a** **4h**(42%) **4i**

## 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-ms calcd for $C_{19}H_{17}O_2FS$ 328.4053, found 328.0935; ir (KBr) 3071, 3018, 2950, 1654, 1536, 1405, 1316, 1233, 1028, 976, 743, 692 $cm^{-1}$. Anal. Calcd for $C_{19}H_{17}O_2FS$ : 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)-4*H*-pyran-4-one (**4a**) (0.034 g, 11 %) was obtained as a minor product.

### 2-Methyl-6-(1-phenylthiobenzyl)-4*H*-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

$MgSO_4$ and chromatographed on $SiO_2$ column. Elution with a mixture of hexane and ethyl acetate (2 : 1) provided 2-methyl-6-(1-phenylthiobenzyl)-4*H*-pyran-4-one (**4a**) (0.200 g, 65 %). **4a** : oil ; $^1$H nmr ($CDCl_3$) 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 $C_{19}H_{16}O_2S$ 308.3994, found 308.0863 ; ir (neat) 3100, 1660, 1630, 1490, 1440, 1400, 930, 880, 750, 700 $cm^{-1}$. Anal. Calcd for $C_{19}H_{16}O_2S$ : C, 74.00 ; H, 5.23. Found : C, 73.79 ; H, 5.28.

**2,3-Dimethyl-6-(1-phenylthiobenzyl)-4*H*-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)-4*H*-pyran-4-one (**4b**) (58 %). **4b** : oil ; $^1$H nmr ($CDCl_3$) 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 $C_{20}H_{18}O_2S$ 322.4262, found 322.1041 ; ir (neat) 3090, 1660, 1620, 1420, 1390, 1160, 940, 740, 700 $cm^{-1}$. Anal. Calcd for $C_{20}H_{18}O_2S$ : C, 74.50 ; H, 5.63. Found : C, 74.33 ; H, 5.71.

**3-Ethyl-2-methyl-6-(1-phenylthiobenzyl)-4*H*-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)-4*H*-pyran-4-one (**4c**) (64 %). **4c** : oil ; $^1$H nmr ($CDCl_3$) 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 $C_{21}H_{20}O_2S$ 336.4530, found 336.1191 ; ir (neat) 2950, 1650, 1610, 1400, 1150, 920, 730, 680 $cm^{-1}$. Anal. Calcd for $C_{21}H_{20}O_2S$ : C, 74.97 ; H, 5.99. Found : C, 74.75 ; H, 6.07.

**2-Phenyl-6-(1-phenylthiobenzyl)-4*H*-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)-4*H*-pyran-4-one (**4d**) (67 %). **4d** : oil ; $^1$H nmr ($CDCl_3$) 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 $C_{24}H_{18}O_2S$ 370.4702, found 370.1046 ; ir (neat) 3000, 1640, 1600, 1430, 1380, 1010, 930, 750, 680

$cm^{-1}$. Anal. Calcd for $C_{24}H_{18}O_2S$ : 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 ; $^1H$ nmr ($CDCl_3$) δ 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 $C_{13}H_{12}O_2$ 200.2358, found 200.0851 ; ir (neat) 2950, 1650, 1600, 1380, 1020, 920, 750, 680 $cm^{-1}$. Anal. Calcd for $C_{13}H_{12}O_2$ : 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 ; $^1H$ nmr ($CDCl_3$) δ 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, 900, 850, 730, 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 ; $^1H$ nmr ($CDCl_3$) δ 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.

**α,α-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 α,α-bis(6-methyl-4*H*-pyran-4-one-2-yl)toluene (**4h**) (42 %). **4h** : mp 95 - 96 ℃ ; $^1$H nmr($CDCl_3$) δ 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.

## ACKNOWLEDGEMENT

This work was supported by the Basic Science Research Institute Program, Ministry of Education(BSRI-96-3422) and the Ministry of Science and Technology.

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Received, 24th July, 1996