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

Bum Tae Kim,*[a] No Kyun Park,[a] Chwang Siek Pak,[a] Myong Sang Kim,[b] and In Howa Jeong,*[b]

[a]Korea Research Institute of Chemical Technology, Daejeon 305-606, Korea

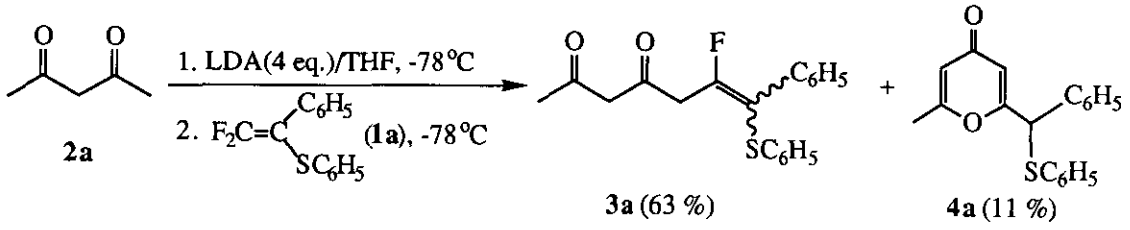
[b]Department of Chemistry, Yonsei University, Wonju 220-710, Korea

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.

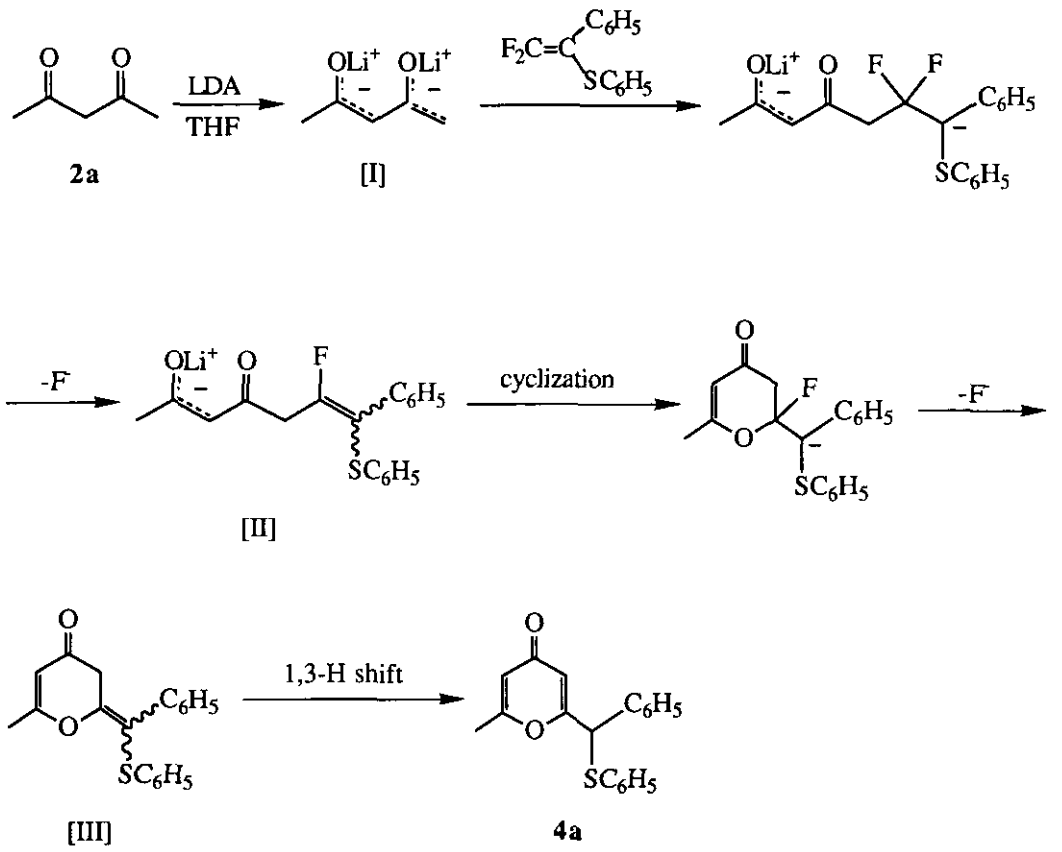
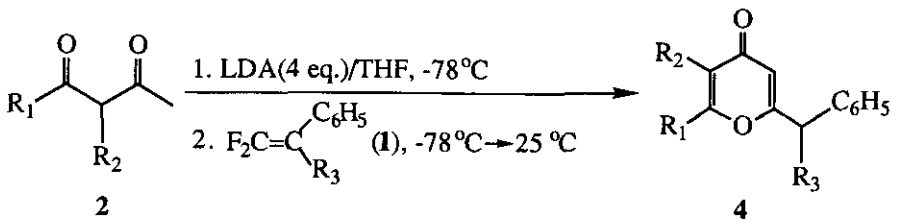


Figure 1. The plausible mechanism for the formation of **4a**

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.

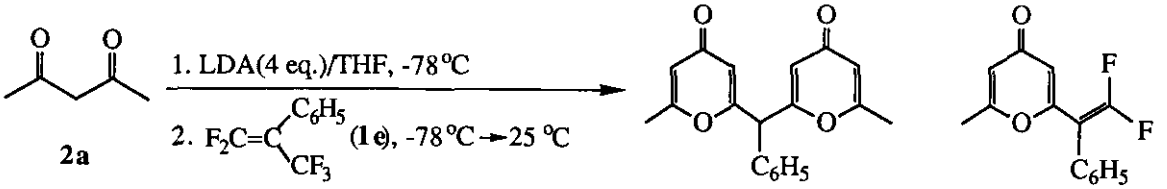
Table 1. Preparation of 4*H*-Pyran-4-one Derivatives (**4**)



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.

REFERENCES

1. (a) R. D. Chambers, "Comprehensive Organic Chemistry", Pergamon Press, Inc., Oxford, 1979. (b) M. Hudlicky and A. E. Pavlath, "Chemistry of Organic Fluorine Compounds II", ACS Monograph 187, 1995.
2. (a) H. F. Koch, W. Tumas, and R. Knoll, *J. Am. Chem. Soc.*, 1981, **103**, 5423. (b) H. F. Koch, J. G. Koch, N. H. Koch, and A. J. Koch, *J. Am. Chem. Soc.*, 1983, **105**, 2388.
3. (a) J. Hine, R. Wiesboek, and O. B. Ramsay, *J. Am. Chem. Soc.*, 1961, **83**, 1222. (b) H. F. Koch and A. J. Kielbania, *J. Am. Chem. Soc.*, 1970, **92**, 729.
4. (a) C. J. M. Stirling, *Acc. Chem. Res.*, 1979, 12, 198. (b) H. F. Koch, J. G. Koch, D. B. Donovan, A. G. Toczko, and A. J. Kielbania, Jr., *J. Am. Chem. Soc.*, 1981, **103**, 5417.
5. (a) Y. Gimbert, A. Moradpour, G. Dive, D. Dehareng, and K. Lahlil, *J. Org. Chem.*, 1993, **58**, 4685. (b) J. Ichikawa, M. Kobayashi, N. Yokota, Y. Noda, and T. Minami, *Tetrahedron*, 1994, **50**, 11637.
6. I. H. Jeong, Y. K. Min, Y. S. Kim, B. T. Kim, and K. Y. Cho, *Tetrahedron Lett.*, 1994, **35**, 7783.
7. B. T. Kim, Y. K. Min, N. K. Park, K. Y. Cho, and I. H. Jeong, *Heterocycles*, 1995, **41**, 641.
8. S. Hayashi, T. Nakai, N. Ishikawa, D. J. Burton, D. G. Naae, and H. S. Kesling, *Chem. Lett.*, 1979, 983.

Received, 24th July, 1996