*Journal of Fluorine Chemistry*, 29 (1985) 445–458



Received: January 30, 1985; accepted: June 17, 1985

# SYNTHESIS OF USEFUL BUILDING BLOCKS FOR MONOFLUORINATED COMPOUNDS DERIVED FROM TRIFLUOROETHENE

Yoshimichi NAKAYAMA, Tomoya KITAZUME * and Nobuo ISHIKAWA*

Department of Chemical Technology, Tokyo Institute of Technology, Ookayama, Meguro-ku, Tokyo 152 (Japan)

## SUMMARY

A synthetic approach to monofluorinated compounds starts from the Friedel-Crafts acylhalogenation of trifluoroethene to give chlorotrifluoroketones and thence trifluorovinyl ketones. These are converted to phenylthio-adducts and thence monofluorinated α,β-unsaturated phenylthioesters, which by reduction afford β-fluoroallylic alcohols.

## INTRODUCTION

The chemistry of fluoroolefins has been developed mainly for the purpose of studying their reactivity [1]. However,with the exception of lithiation of trifluoroethene [2] or chlorotrifluoroethene [2], only a few reports have focussed on the synthetic utility of fluoroolefins in the preparation of the wide variety of monofluorinated compounds [3-8] of interest as bioactive materials. We recently outlined a convenient Friedel-Crafts acylhalogenation of trifluoroethene and its Claisen-type condensation under acidic conditions [9-10].

In this paper, we describe the conversion of the derived chlorotrifluoroalkanones into alkyl trifluorovinyl ketones which are useful building blocks for valuable monofluorinated compounds.

0022-1139/85/$3.30 

RESULTS AND DISCUSSION

Our preparation of alkyl trifluorovinyl ketones is simpler than that reported by other workers [11]. Thus, 4-chloro-3,4,4-trifluoro-2-butanone (1a) [9] was allowed to react with a diglyme solution of triethylamine to produce methyl trifluorovinyl ketone (2a). The reaction proceeded smoothly at -78 C, and the product was isolated by a trap to trap system under dynamic vacuum. The material is stable enough to be isolated and can be stored for several weeks in the ice-box under a nitrogen atmosphere.

The trifluorovinyl ketone structure was finally established by NMR spectroscopy. The assignment of the NMR signals was done as shown in Fig. I.

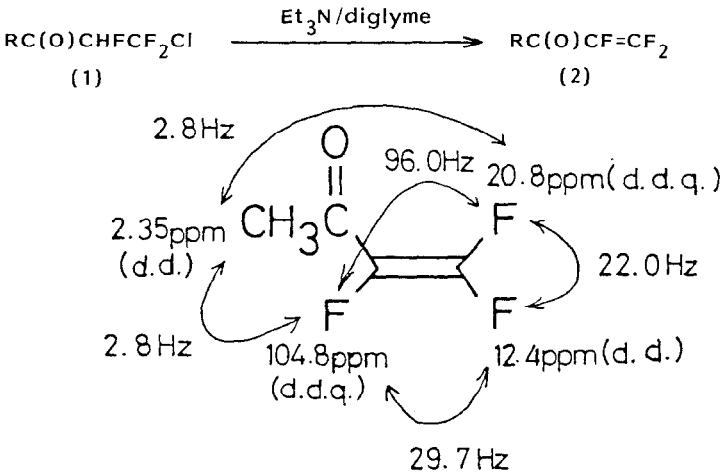



Fig. 1 The $^{1}H$ and $^{19}F$ NMR spectra of (2a)

In our continuing programme to synthesise monofluorinated compounds [8-10], trifluorovinyl compounds are useful building blocks, being susceptible to attack by a wide variety of nucleophiles.

2-Phenylthio-1,2,2-trifluoroethyl alkyl ketones (3a,3b) were prepared by the Michael addition of thiophenol to trifluorovinyl ketones made in situ. They are stable compounds, but smoothly produced the corresponding alkyl vinyl compounds by the elimination of HF using a $Et_3N$/i-PrOH system. 1-Phenylthio-1,2-difluoro-1-buten-3-one (4a) and 1-phenylthio-1,2-difluoro-1-penten-3-one (4b) were thus obtained in 93% (4a) and 88% (4b) yield. The E/Z ratio of the products was determined by $^{19}F$ NMR, the identification being based on the well-established coupling constants for difluorovinyl compounds (Table 1).

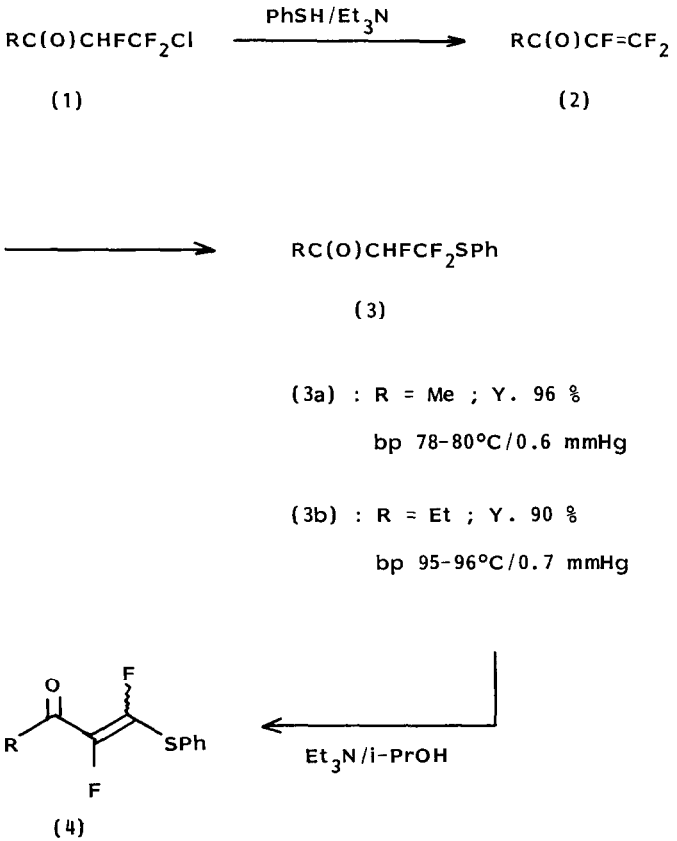


TABLE 1

Dehydrofluorination of $RC(O)CHFCF_2SPh$ (3)

| Product No. | R | Yield(%) | E/Z ratio | Bp (°C/mmHg) |
|---|---|---|---|---|
| 4a (nc) | Me | 96 | 27/73 | 91-95/0.2 |
| 4b (nc) | Et | 98 | 30/70 | 101-105/0.5 |

TABLE 4

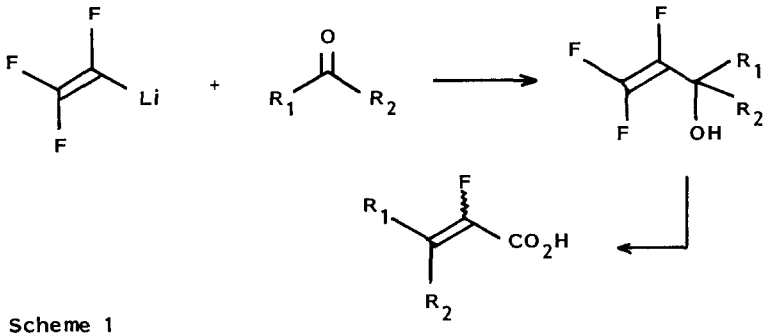
Reduction of $RC(CH_3)=CFC(O)SPh$ (8) with $NaBH_4$

| Product No. | R (E/Z ratio) | Yield (%)[a] | E/Z ratio | Bp (°C/mmHg) |
|---|---|---|---|---|
| 9a | Me | 67 (85) | | 69-72/48 |
| 9b (nc) | i-Pr (26/74) | 67 (82) | 32/68 | 70-73/21 |
| 9c (nc)[b] | Ph (20/80) | 81 (97) | 11/89 | |

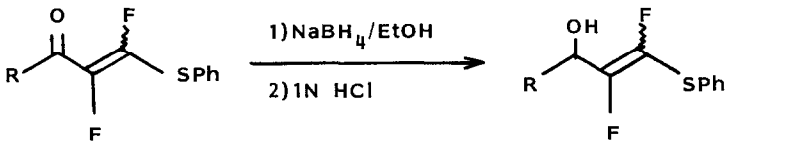
[a] Yields in parentheses are determined by $^{19}F$ NMR signal intensities using $PhCF_3$ as an internal standard. [b] Isolated by column chromatography.

## Preparation of monofluorinated α,β-unsaturated phenylthioesters (8)

The rearrangement of carbinols to carboxylic acids shown in Scheme 1 has been reported by J. F. Normant and co-workers [3-6]. In our building block system,we found that the reduction of compounds (4a) and (4b) with $NaBH_4$ readily proceeded to the formation of vinylic carbinols (5a, 5b). Acid hydrolysis then gave monofluorinated α,β-unsaturated phenylthioesters (6a,6b) thus providing a route to functionalized monofluoroorganic compounds, which can serve as building blocks for bioactive monofluorinated materials.



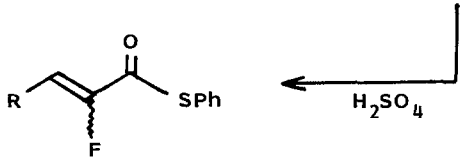
Scheme 1



(4)

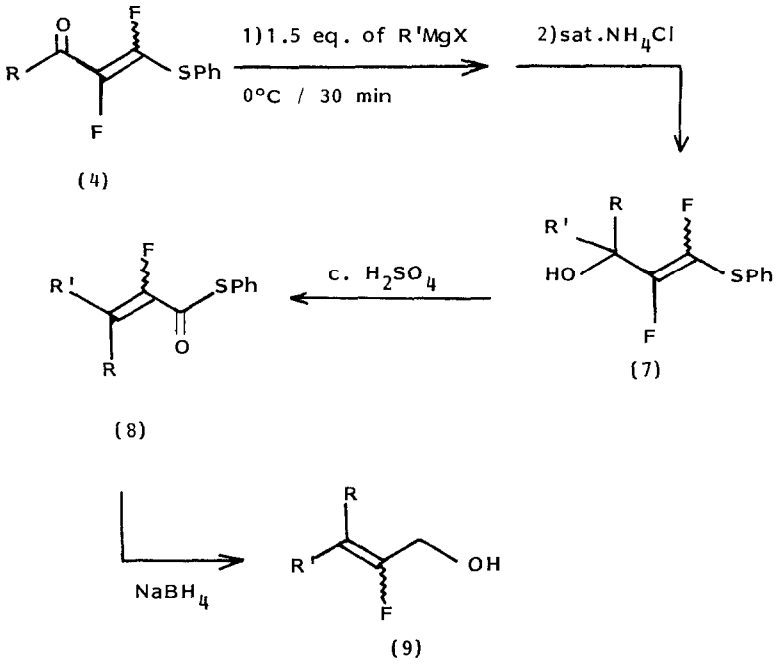
(5a) R = Me ; Y. 95 %

(5b) R = Et ; Y. 90 %



(6) (See Table 3)

Grignard reagents easily attacked the carbonyl group of compounds (4) to give other carbinol precursors for monofluorinated phenylthioesters. The Grignard-type reactions appear to be particularly efficient for the formation of carbinols of type 7 (Table 2). The rearrangement of these carbinols to the title materials (8) with concentrated sulphuric acid, or heat, proceeded quite readily (Table 3).




(4) (7) (8) (9)

Preparation of β-fluorinated allylic alcohols (9)

As it is well known that allylic alcohols are useful synthetic tools [12],and so we attempted the reduction of the fluorinated phenylthioester group. For this purpose, $NaBH_4$ was most efficient and it readily reduced the thioester to form the allylic alcohols (9) having a fluorine atom carried on the carbon-carbon double bond (Table 4).

TABLE 2

Reaction of RC(O)CF=CFSPh (4) with R'MgX

| Product NO | R | R'MgX | Solvent | Yield (%)[a] |
|---|---|---|---|---|
| 7a (nc) | Me | MeMgI | $Et_2O$ | 98 (100) |
| 7b (nc) | Me | EtMgBr | $Et_2O$ | 98 (100) |
| | Me | EtMgBr | THF | 48 (50) |
| | Et | MeMgI | $Et_2O$ | 98 (100) |
| 7c (nc) | Me | PhMgBr | THF | 96 (98) |
| 7d (nc) | Me | i-PrMgCl | $Et_2O$ | 58 (62) |
| 7e (nc) | Et | PhMgBr | THF | 98 (100) |
| 7f (nc) | Et | EtMgBr | $Et_2O$ | 98 (100) |

[a] Yields in parentheses are based on the signal intensities of $^{19}F$ NMR using $PhCF_3$ as an internal standard.

TABLE 3

Preparation of α,β-unsaturated thiol esters (6) or (8) from carbinols (7)

| Product No. | R | R' | Method[b] | Yield[a] (%) | E/Z ratio of (6) or (8) |
|---|---|---|---|---|---|
| 6a (nc) | Me | H | B | 82 (89) | 2/98 |
| 6b (nc) | Et | H | B | 63 (70) | 2/98 |
| 8a (nc) | Me | Me | A | 77 (82) | |
| 8b (nc) | Me | Et | A | 85 (95) | 31/69 |
| | Me | Et | B | 70 (75) | 39/61 |
| 8c (nc) | Me | Ph | A | 64 (79) | 31/69 |
| 8d (nc) | Me | i-Pr | A | 80 (95) | 26/74 |
| 8e (nc) | Et | Ph | A | 55 (71) | 48/52 |
| 8f (nc) | Et | Et | A | 69 (75) | |

[a] Yields in parentheses are based on the signal intensities of $^{19}F$ NMR signal using $PhCF_3$ as an internal standard. [b] Method A : Δ (130-150°C) ; Method B : conc. $H_2SO_4$.

TABLE 5

$^1H$ and $^{19}F$ NMR spectral data for $RC(O)CF_A{=}CF_BSPh$ (4)[a]

| | R | Chemical shift (δ ppm) | |
|---|---|---|---|
| | | $^{19}F$ NMR (neat) | $^1H$ NMR (in $CCl_4$) |
| 4a (nc) | Me | (E) 63.2 ($F_A$, s) | 2.34 ($CH_3$, d) |
| | | | 7.2-7.7 (Ar-H, m) |
| | | 22.3 ($F_B$, q : $J_{F_B\text{-}CH_3}$ = 4 Hz) | |
| | | (Z) 69.8 ($F_A$, d,q : $J_{F_A\text{-}F_B}$ = 133 Hz, $J_{F_A\text{-}CH_3}$ = 4 Hz) | 2.27 ($CH_3$, d,d) |
| | | 32.2 ($F_B$, d,q : $J_{F_B\text{-}CH_3}$ = 0.4 Hz) | |
| 4b (nc) | Et | (E) 65.5 ($F_A$, s) | 1.15 ($CH_3$, t), 2.65 ($CH_2$, m) |
| | | | 7.2-7.7 (Ar-H, m) |
| | | 22.5 ($F_B$, q : $J_{F_B\text{-}CH_3}$ = 3 Hz) | |
| | | (Z) 71.1 ($F_A$, d : $J_{F_A\text{-}F_B}$ = 138 Hz) | 1.09 ($CH_3$, t) |
| | | 33.4 ($F_B$, d,t : $J_{F_B\text{-}CH_3}$ = 3 Hz) | |

[a] The $^1H$ (internal $Me_4Si$) and $^{19}F$ (external $CF_3CO_2H$) NMR spectra were recorded by using a Varian EM-390 spectrometer.

TABLE 6

$^{1}H$ and $^{19}F$ NMR spectral data for RR'C=CFC(O)SPh (6) or (8)

| Product No. | Chemical Shift (δppm) | |
|---|---|---|
| | $^{19}F$ NMR (neat) | $^{1}H$ NMR (in $CCl_4$) |
| 8a | 48.2 (q,q : $J_{F-H}$ = 4.2 Hz, $J_{F-H}$ = 3.3 Hz) | 1.80, 2.01 ($CH_3$, d), 7.37 (Ar-H, s) |
| 8b | 48.3 (E, t,q : $J_{F-H}$ = 4.5 Hz, $J_{F-H}$ = 1.7 Hz) | 0.99 ($CH_3$, t), 1.81 ($CH_3$, d), 2.46 ($CH_2$, d,q), 7.40 (Ar-H, s) |
| | 49.7 (Z, t,q : $J_{F-H}$ = 3.6 Hz, $J_{F-H}$ = 3.2 Hz) | 1.04 ($CH_3$, t), 2.00 ($CH_3$, d) 2.21 ($CH_2$, d,q), 7.40 (Ar-H, s) |
| 8d | 46.8 (E, br : $J_{F-H}$ = 4.5 Hz, $J_{F-H}$ = 3.0 Hz) | 1.02 ($CH_3$, d), 1.71 ($CH_3$, d) 3.76 (CH, d,sep), 7.33 (Ar-H, s) |
| | 44.0 (Z, q : $J_{F-H}$ = 3.8 Hz, $J_{F-H}$ = 1.1 Hz) | 1.02 ($CH_3$, d), 1.91 ($CH_3$, d) 3.08 (CH, d,sep), 7.33 (Ar-H, s) |
| 6a | 51.2 (d,q : $J_{F-H}$ = 34 Hz, $J_{F-H}$ = 3.0 Hz) | 1.78 ($CH_3$, d,d), 6.03 (H, d,d) 7.40 (Ar-H, s) |
| 8e | 46.0 (t : $J_{F-H}$ = 3.8 Hz) | 1.02 ($CH_3$, t), 2.56 ($CH_2$, d,q) 7.1-7.4 (Ar-H, m), 7.39 (Ar-H, s) |
| 6b | 51.0 (d,t : $J_{F-H}$ = 35 Hz, $J_{F-H}$ = 2.3 Hz) | 1.05 ($CH_3$, t), 2.22 ($CH_2$, d,d,q) 5.99 (H, d,q), 7.39 (Ar-H, s) |

TABLE 7

$^{1}H$ and $^{19}F$ NMR spectral data for $RC(CH_3)=CFCH_2OH$ (9)

| R | Chemical shift ($\delta$ ppm) | |
|---|---|---|
| | $^{19}F$ NMR (neat) | $^{1}H$ NMR (in $CCl_4$) |
| i-Pr (9b) | 38.7 (E, t : $J_{F-H}$ = 23 Hz, $J_{F-H}$ = 2.4 Hz) | 1.05 ($CH_3$, d), 1.60 ($CH_3$, d) |
| | | 3.55 (OH, br), 4.09 ($CH_2$, d) |
| | 39.8 (Z, t : $J_{F-H}$ = 23 Hz, $J_{F-H}$ = 3.0 Hz) | 2.67 (CH, d,sep), 3.00 (CH, sep) |
| | | 4.11 ($CH_2$, d) |
| Ph (9c) | 36.3 (E, t : $J_{F-H}$ = 23 Hz, $J_{F-H}$ = 3.0 Hz) | 1.96 ($CH_3$, d), 3.09 (OH, br) |
| | | 4.26 ($CH_2$, d), 7.25 (Ar-H, s) |
| | 37.0 (Z, t : $J_{F-H}$ = 23 Hz, $J_{F-H}$ = 3.0 Hz) | 4.00 ($CH_2$, d) |

## EXPERIMENTAL

### Methyl trifluorovinyl ketone (2a)

Into a solution of 4-chloro-3,4,4-trifluoro-2-butanone (1a) (8.03 g, 50 mmol) in freshly dried diglyme (30 ml) cooled with an ice-water bath, was added triethylamine (5.05 g, 50 mmol). After the mixture had been allowed to warm to room temperature,the whole solution was stirred for 30 min at that temperature. Methyl trifluorovinyl ketone (5.30 g, yield 85 %) was collected under dynamic vacuum in a trap cooled with a dry-ice acetone bath.

### 4-Phenylthio-3,4,4-trifluoro-2-butanone (3a)(nc)

Triethylamine (5.06 g, 50 mmol) in dichloromethane (30 ml) was added to a solution of 4-chloro-3,4,4,-trifluoro-2-butanone (1a) (8.03 g, 50 mmol) and thiophenol (5.51 g, 50 mmol) in dichloromethane (70 ml) cooled with an ice-water bath. After the mixture had been stirred for 30 min at room temperature,the whole was poured into water. The separated organic layer was dried over anhydrous magnesium sulfate and then the solvent was removed. Distillation gave 4-phenylthio-3,4,4-trifluoro-2-butanone in a yield of 96 % (11.2 g), bp 78-80 C/0.6 mmHg.

### 1-Phenylthio-1,2-difluoro-1-buten-3-one (4a)(nc)

Triethylamine (3.03 g, 30 mmol) was added to a solution of 4-phenylthio-3,4,4-trifluoro-2-butanone (3a) (7.02 g, 30 mmol) in 2-propanol (50 ml) cooled with an ice-water bath. The mixture was stirred for 30 min at room temperature,and the whole was then poured into water. Oily material was extracted with diethyl ether, and then the ethereal layer was dried over anhydrous magnesium sulfate. After the solvent was removed,the residue was distilled in vacuo,giving 1-phenylthio-1,2-difluoro-1-buten-3-one in a yield of 96 % (6.14 g), bp 91-95 C/0.2 mmHg.

1-Phenylthio-1,2-difluoro-3-hydroxy-1-butene (5a)(nc)

Into a suspension of $NaBH_4$(0.19 g, 5 mmol) and ethanol (10 ml) cooled with an ice-water bath, 1-phenylthio-1,2-difluoro-1-buten-3-one (4a)(2.14 g, 10 mmol) was added. After the mixture was stirred for 1h at that temperature, the reaction was quenched with 1N HCl. Oily material was extracted with diethyl ether,and then the ethereal layer was washed with water. The solvent was removed, and 1-phenylthio-1,2-difluoro-3-hydroxy-1-butene (5a) was purified by column chromatography using a mixture solution of n-hexane-diethyl ether (1:1) as an eluent (yield 95 %).

1-Phenylthio-1,2-difluoro-3-hydroxy-3-methyl-1-butene (7a)(nc)

Into a solution of MeMgI prepared from MeI (4.26 g, 30 mmol) and magnesium (0.8 g, 33 mg-atom) in freshly dried diethyl ether (50 ml), was added 1-phenylthio-1,2-difluoro-1-buten-3-one (4a) (4.28 g, 20 mmol) in dry diethyl ether (10 ml) at 0-5 C. The mixture was stirred for 30 min, and was then quenched with saturated $NH_4Cl$ solution. Oily material was extracted with diethyl ether, and then the ethereal layer was dried over magnesium sulfate. After the solvent was removed, the carbinol was purified by column chromatography using the mixture solution of n-hexane-diethyl ether (1:1) as an eluent (4.51 g, yield: 98 %).

2-Fluoro-3-methyl-2-butenoic acid phenylthio ester (8a)

One drop of conc.$H_2SO_4$ was added to 1-phenylthio-1,2-difluoro-3-hydroxy-3-methyl-1-butene (7a) (2.44 g, 10 mmol). After 1 min of stirring, triethylamine (3.0 g, 30 mmol) in n-hexane (30 ml) was added to the mixture solution. After filtration of the precipitate, the mixture was dried over magnesium sulfate. After the solvent was removed, the product was purified by column chromatography using n-hexane as an eluent (1.57 g, yield: 70 %).

2-Fluoroprenol (9a)

Into a suspension of $NaBH_4$ (0.45 g, 12 mmol) in ethanol (10 ml) cooled with an ice-water bath,2-fluoro-3-methyl-2-butenoic acid phenylthio ester (8a)(2.10 g, 10 mmol) was added slowly. After 2h of stirring, the mixture was quenched with 1N HCl solution. Oily material was extracted with diethyl ether and then the ethereal extract was dried over magnesium sulfate. After the solvent had been removed, distillation gave 2-fluoroprenol (9a) (0.37 g, 36 %), bp 69-72°C/48 mmHg.

REFERENCES


1 See for example, M, Hudlicky, Chemistry of Organic Fluorine Compounds, Wiley, N.Y., (1976).
2 M. Schlosser, Tetrahedron, 34 (1978) 3.
3 J. F. Normant, J. P. Foulon, D. Masure, R. Sauvetre and J. Villieras, Synthesis, (1975) 122.
4 R. Sauvetre, D. Masure, C. Chuit and J. F. Normant, Synthesis, (1978) 128.
5 C. Chuit, R. Sauvetre, D. Masure, M. Baudry, J. F. Normant and J. Villieras, J. Chem. Res., (1977) 104.
6 D. Masure, R. Sauvetre, J. F. Normant and J. Villieras, Synthesis, (1976) 761.
7 D. E. Bergstrom, M. W. Ng and J. J. Wong, J. Org. Chem., 48 (1983) 1902.
8 N. Ishikawa, A. Takaoka, Chem. Lett., (1981) 107.
9 N. Ishikawa, H. Iwakiri, K. Edamura, S. Kubota, Bull. Chem. Soc. Jpn., 54 (1981) 832.
10 N. Ishikawa, A. Takaoka, H. Iwakiri, S. Kubota, S. R. F. Kagaruki, Chem. Lett., (1980) 1107.
11 I. L. Knunyants, R. N. Sterlin, L. N. Pinkina and B. L. Dyatkin, Izv. Akad. Nauk. SSSR, Ser. Khim., (1958) 296.
12 S. G. Wilkinson, Comprehensive Organic Chemistry, ed. by J. F. Stoddart, Vol 1, Pergamon Press, Oxford, 1979, p 579.