93. Fluorine-Containing Organozinc Reagents

Part I

A Simple Synthesis of 2,2-Dichloro-3,3,3-trifluoropropanol

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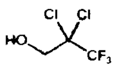
The title compound **1**, which can be regarded as a synthetic equivalent of substituted 1,1,1-trifluoroacetone **2**, is prepared by Zn-induced reductive addition of 1,1,1-trichloro-2,2,2-trifluoroethane (**3**) to formaldehyde (**4**). A brief survey of the scope of this C–C-bond formation leading to a variety of new CF_3-containing synthetic building blocks is also given.

Fluorine-containing drugs and pesticides, frequently made available by use of new reagents and improved techniques for the selective introduction of fluorine, have achieved an increasing interest in modern bioorganic chemistry [1] [2]. Among other effects, the replacement of hydrogen by fluorine usually increases lipid solubility, thereby enhancing the rates of absorption and transport of active compounds *in vivo*. In fact, the change of lipophilicity in a given substrate may often be the main source of an increasing therapeutic efficacy. In particular, the CF_3 group is among the most lipophilic of all common substituents, and, therefore, the selective introduction of CF_3 groups into bioactive molecules became a major target in fluoroorganic chemistry. This inherent synthetic problem may either be solved by direct fluorination, by CF_3 substitution, or by use of CF_3-containing building blocks. Both, direct fluorination methodology and CF_3-substitution reactions are of very limited applicability, and thus the building-block strategy proves to be of a particular significance. However, besides CF_3COOH and benzotrifluoride, which are as yet the most important starting materials for the synthesis of CF_3-containing substrates, there is a remarkable lack of inexpensive and versatile CF_3-containing synthetic building blocks.

In 1966, the title compound **1** was prepared for the first time by reacting HF and 1,1-dichloro-2,2-difluoroethylene with paraformaldehyde [3]. Surprisingly, this simple polyhalogenated alcohol **1**, which can be regarded as a synthetic equivalent of **2**, a derivative of 1,1,1-trifluoroactone, never since got any scientific interest.

As part of our search for inexpensive and versatile CF_3-containing synthetic building blocks, we tried to synthesize alcohol **1** according to [3]. Analysis of the reaction mixture



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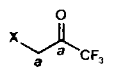

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showed only traces of the anticipated compound **1**, and in our hands, all attempts to isolate **1** in its pure form failed. Therefore, we focused our interest on the readily available 1,1,1-trichloro-2,2,2-trifluoroethane (**3**), of which various organometallic derivatives have already been reported in the literature. Based on the fact, that several solvent complexes of CF_3CCl_2ZnCl have already been isolated [4] [5], we decided to study the C–C-bond formation by reacting CF_3CCl_3 (**3**) with an appropriate electrophilic C-atom in the presence of metallic Zn¹).

When equimolar amounts of **3**, paraformaldehyde as a source for formaldehyde (**4**), and metallic Zn are allowed to react at room temperature in DMF, a moderately exothermic reaction occurs after a certain induction period, which in particular seems to correspond to the activity of the utilized Zn powder. Under the given reaction conditions (*cf. Scheme 1* and *Exper. Part*) the desired alcohol **1**, after hydrolysis of the reaction mixture and distillation, can be isolated in high yield²). The highly volatile, pure alcohol **1**, which has a strong odour of essential oils, crystallizes in long, colourless needles (m.p. 61°–62°; b.p. 100°–110° (atmospheric pressure)).

Scheme 1

$$\underset{\mathbf{3}}{CF_3CCl_3} + \underset{\mathbf{4}}{HCHO} \xrightarrow[\text{2) aq. HCl}]{\text{1) Zn, DMF, r.t., 3d}} \underset{\mathbf{1}\ (87\%)}{CF_3CCl_2CH_2OH}$$

Recent publications indicate significant improvement of heterogeneous organometallic reactions by using ultrasonic irradiation (*cf.* [8] and lit. cited therein). In contrast to *Kitazume* and *Ishikawa* [9] who found that the reductive coupling of perfluoroalkyl iodides with aldehydes and ketones only occurs with the aid of ultrasonic irradiation, all our experiments run perfectly under standard thermal conditions. Besides that, only moderate effects were observed by changing the reaction conditions (see *Table 1*). Additionally, we found that the conditions of ultrasonic irradiation were much more difficult to reproduce than those of conventional metal activation.

Table 1. *Variations of Reaction Conditions for the Synthesis of* **1** *(cf. Scheme 1)*

Time [h]	Temp. [°]	Stirring[a])	Ultrasound[b])	Yield [%]
60	*ca.* 20	magnetic	–	87
16	*ca.* 20	mechanic	–	46
16	*ca.* 20	mechanic	38 kHz	64
16	*ca.* 20	mechanic	22 kHz	74

[a]) Magnetic and mechanic stirring at 1550–2000 rpm (10-mmol runs).

[b]) Ultrasound laboratory cleaner *BL 14* (*Elga AG*, Biel).

To achieve more flexibility for using **1** as a CF_3-containing, synthetic building block, we have prepared some easily accessible derivatives of **1** (*Scheme 2*). Protection of the relatively acidic OH function of **1** ($pK_a \geqslant 12$ in 80% methylcellosolve) can be achieved by benzylation (**1**→**5**), tosylation (**1**→**6**) or acylation (**1**→**7**). Zn-induced reductive elimi-

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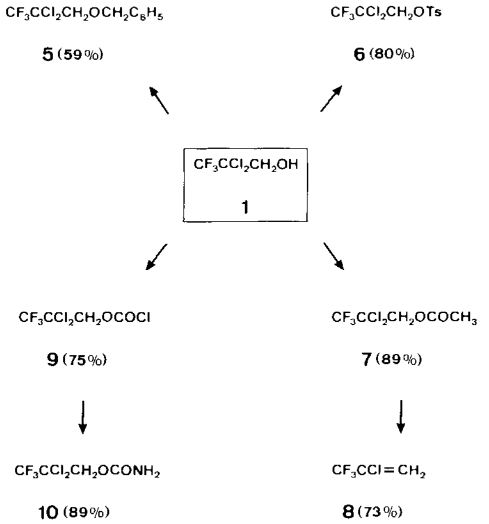
[1]) Very little is known about such a Zn-induced reductive coupling reaction of **3** [6] [7], but during preparation of this manuscript, we learned from Dr. *T. Hiyama* (Sagami Chemical Research Center, Japan) about their independent work on this subject. The author would like to thank Dr. *T. Hiyama* for two preprints of papers, which were submitted to *Tetrahedron Lett.* for publication.

[2]) According to this procedure, **1** can easily be prepared in kilogram quantities.

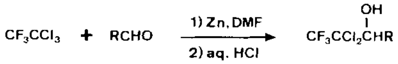
Scheme 2



nation at the ester **7** leads to the olefin **8** which, in turn, can be regarded as a synthetic equivalent of 1,1,1-trifluoroacetone. Treatment of **1** with $COCl_2$ yields the chloroformate **9** which can easily be transformed to **10** by aminolysis[3]).

An extension of our synthetic conception shows that, under the same conditions as for the synthesis of **1**, the CF_3CCl_2 group can be added to a wide variety of substituted aliphatic and aromatic aldehydes. A list of representative examples is given in *Table 2* (for a more complete study, *cf.* [10]). As indicated in *Table 2 (Entry b–d)*, selective 1,2-addition has been found for α,β-unsaturated aldehydes. However, for both ketones and carboxylic-acid derivatives, all our attempts to prepare any comparable addition product failed.

Table 2. *Zn-Induced Reductive Addition of CF_3CCl_3 to Various Aldehydes* (see also [10])



$$CF_3CCl_3 + RCHO \xrightarrow[\text{2) aq. HCl}]{\text{1) Zn, DMF}} CF_3CCl_2\overset{OH}{\overset{|}{C}}HR$$

Entry	R	Reaction conditions[a])	Product (Yield [%])
a	$(CH_3)_2CH$	r.t./2 d	**11** (80)
b	$CH_2=CH$	r.t./2 d	**12** (60)
c	$(CH_3)_2C=CH$	r.t./1 d	**13** (63)
d	PhCH=CH	r.t./3.5 h	**14** (69)
e	Ph	r.t./1 d	**15** (95)
f	2-Furyl	r.t./3 d	**16** (98)

[a]) Non-optimized reaction conditions.

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[3]) Application of **1** and its derivatives for the construction of new CF_3-containing molecules are currently under investigation.

Concerning the reaction mechanism of the described Zn-induced reductive C–C bond formation, it is as yet not possible to decide, whether radical or ionic processes are taking place[4]).

I am especially indebted to Dr. *Ch. Angst* and to Dr. *H. Greuter* for helpful discussions, and I like to thank Miss *B. Haefeli* for her skillful assistance in the laboratory. I am grateful to my colleagues in the Physical and Analytical Departments for performing the spectral and elemental analyses.

Experimental Part

General. Unless otherwise noted, materials and solvents were obtained from commercial suppliers and were used without further purification. All reactions were performed under Ar. Chemical yields (except for **1**) refer to non-optimized reaction conditions. Zn powder (*Riedel de Haen, p.a.*) was activated according to *Fieser* and *Fieser* [11]. Paraformaldehyde was purchased from *Merck* (for synthesis) and DMF (*Fluka AG, puriss.*) was stored over activated molecular sieve (4 Å). Flash chromatography (FC; following the method described by *Still et al.* [12]) was performed with *Merck* silica gel *60* (230–400 mesh ASTM). Melting points (m.p.): *Tottoli* capillary melting-point apparatus (uncorrected). IR ($\tilde{\nu}$ [cm^{-1}]): *Perkin-Elmer IR 298*. ^{1}H-NMR, ^{13}C-NMR, and ^{19}F-NMR (δ [ppm] relative to internal TMS or $CFCl_3$ (^{19}F-NMR); in $CDCl_3$ unless otherwise noted; *J* [Hz] = apparent coupling constant): *Variant T 60*, *Varian HA 100*, *Bruker WM 250*, or *Bruker WM 400* spectrometer (for ^{1}H-NMR) and *Varian XL 100* or *Varian XL 300* (for ^{13}C-NMR and ^{19}F-NMR). MS: *Varian CH-7 MAT* and *CEC 21-110* at 70 eV.

1. *2,2-Dichloro-3,3,3-trifluoropropanol* (**1**). A mixture of 3.0 g (0.10 mol) of *paraformaldehyde* (**4**), 20.6 g (0.11 mol) of *1,1,1-trichloro-2,2,2-trifluoroethane* (**3**), and 8.17 g (0.125 g-atom) of freshly activated Zn powder in 180 ml of dry DMF was vigorously stirred under Ar at r.t. After an induction period of 30–60 min, a moderately exothermic reaction occurred and the dissolution of the Zn began. Most of the Zn was consumed after 60 h, and the mixture was poured on a stirred mixture of ice, 10% aq. HCl, and Et_2O. After additional 30 min, the separated org. layer was washed successively with 2% aq. HCl and brine, dried ($MgSO_4$), and concentrated *in vacuo* at 0°. Distillation of the yellow, oily residue at 100–110°/760 Torr afforded 16.0 g (87%) of **1**: colourless needles. M.p. 61–62°. IR ($CHCl_3$): 3595*m*, 3350*m* (br.), 2980*m*, 2930*w*, 2870*w*, 1450*w*, 1370*m*, 1295 (sh), 1280*s*, 1265*s*, 1185*s*, 1095*s*, 1030*s*, 1015*s*, 940*m*, 890*s*, 820*m*. ^{1}H-NMR (250 MHz, $CDCl_3$): 4.14 (*d*, *J* = 7.0, CH_2); 2.52 (*t*, *J* = 7.0, OH). ^{13}C-NMR (25 MHz, $CDCl_3$): 122.0 (*q*, *J*(F,C) = 283, C(3)); 84.6 (*q*, *J*(F,C) = 34, C(2)); 68.3 (*s*, C(1)). ^{19}F-NMR (94 MHz, $CDCl_3$): −77.3 (*s*). MS: 166, 164, 162 ($M^{+\cdot}$ − HF), 136, 134, 132 ($M^{+\cdot}$ − HF − HCHO). Anal. calc. for $C_3H_3Cl_2F_3O$ (182.96): C 19.69, H 1.65, F 31.15; found: C 19.95, H 1.79, F 31.15.

2. *Benzyl 2,2-Dichloro-3,3,3-trifluoropropyl Ether* (**5**). Following the above procedure, 25.6 g (0.15 mol) of $PhCH_2Br$ were added directly after the 60-h reaction period, and for additional 2 h the mixture was heated at 120°. After dilution with H_2O, the product was extracted with Et_2O and purified by FC (CH_2Cl_2). Distillation at 140°/12 Torr afforded 16.2 g (59%) of **5** as a colourless oil. ^{1}H-NMR (60 MHz, $CDCl_3$): 7.4 (br. *s*, 5 arom. H); 4.7 (*s*, $C_6H_5CH_2$); 4.0 (br. *s*, CH_2CCl_2).

3. *2,2-Dichloro-3,3,3-trifluoropropyl* p-*Toluenesulfonate* (**6**). To a suspension of 7.9 g (42 mmol) of TsCl in 40 ml of Et_2O were added 10.0 g (55 mmol) of **1** followed by 8.4 g (83 mmol) of Et_3N. After 3 d stirring at r.t., 0.75 ml of H_2O were added dropwise and stirring was continued for an additional 2 h. Then the mixture was washed successively with 5% aq. tartaric acid, 1N aq. $NaHCO_3$, and H_2O, dried ($MgSO_4$), and concentrated *in vacuo*. Distillation of the orange, oily residue at 180°/0.01 Torr yielded 11.1 g (80%) of **6**: colourless crystals. M.p. 39–41°. ^{1}H-NMR (60 MHz, $CDCl_3$): 7.7 (*AA'BB'*-system, 4 arom. H); 4.5 (br. *s*, CH_2); 2.5 (*s*, CH_3).

4. *2,2-Dichloro-3,3,3-trifluoropropyl Acetate* (**7**). A mixture of 50.0 g (0.27 mol) of **1**, 30.6 g (0.30 mol) of Ac_2O, and 25.9 g (0.33 mol) of pyridine was stirred over night at r.t. Workup was achieved by pouring on ice, adding of aq. HCl, and extracting with Et_2O. The washed and dried ($MgSO_4$) org. layer was then concentrated *in vacuo*

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[4]) To get more insight into this particular coupling mechanism, we have isolated possible reaction intermediates. Structure elucidation and analysis of their reactivity are currently under investigation and will be the subject of a subsequent publication.

Distillation of the orange, oily residue at 67–72°/90 Torr afforded 54.6 g (89%) of **7** as a colourless oil. ^{1}H-NMR (60 MHz, CDCl$_3$): 4.5 (br. *s*, CH$_2$); 2.15 (*s*, CH$_3$). ^{13}C-NMR (25 MHz, CDCl$_3$): 169.4 (*s*, CO); 121.8 (*q*, *J*(F,C) = 283, C(3)); 81.4 (*q*, *J*(F,C) = 35, C(2)); 66.4 (*s*, C(1)); 20.4 (*s*, CH$_3$).

5. *2-Chloro-1,1,1-trifluoropropene* (**8**). For the synthesis of **8**, a three-necked round-bottom flask was fitted with a dropping funnel and a reflux condenser. The top of the condenser was directly connected to a distillation apparatus, whose receiver was cooled with dry ice/acetone. During dropwise addition of 22.5 g (0.1 mol) of **7** to a suspension of 8.0 g (0.12 g-atom) of freshly activated Zn in 70 ml of refluxing EtOH, an exothermic reaction occurred, and the product began to distill. Redistillation of the crude material at 15°/760 Torr (14–15° [13]: b.p.) afforded 9.5 g (73%) of **8** as a mobile, colourless liquid. ^{1}H-NMR (60 MHz, CDCl$_3$): 6.05 (*m*, 1 H); 5.75 (*m*, 1 H).

6. *2,2-Dichloro-3,3,3-trifluoropropyl Chloroformate* (**9**). During 3.5 h, 26.0 g (0.26 mol) of COCl$_2$ were passed through an ice-cold soln. of 45.8 g (0.25 mol) of **1** in 175 ml of CH$_2$Cl$_2$. Afterwards, 19.8 g (0.25 mol) of pyridine, dissolved in 25 ml of CH$_2$Cl$_2$, were added dropwise at −20°. The mixture was stirred over night at r.t. and then flushed with N$_2$. After pouring the mixture on ice-cold H$_2$O, the org. layer was separated, washed, and dried (MgSO$_4$). Distillation of the CH$_2$Cl$_2$ extract by using a *Vigreux* column yielded 45.7 g (75%) of **9** as a colourless oil. B.p. 36°/20 Torr. ^{1}H-NMR (60 MHz, CDCl$_3$): 4.8 (*s*, CH$_2$). ^{13}C-NMR (25 MHz, CDCl$_3$): 153.1 (*s*, CO); 121.5 (*q*, *J*(F,C) = 284, C(3)); 80.5 (*q*, *J*(F,C) = 36, C(2)); 70.0 (*s*, C(1)).

7. *2,2-Dichloro-3,3,3-trifluoropropyl Carbamate* (**10**). A soln. of 60.0 g (0.24 mol) of **9** in 20 ml of toluene was dropped into 335 ml of 25% aq. NH$_3$ at 0°. After stirring at r.t. for 2 h, the product was extracted with Et$_2$O, washed, and dried (MgSO$_4$). The crude crystalline material was recrystallized from hot petroleum ether yielding 49.1 g (89%) of **10**: colourless crystals. M.p. 56–57°. ^{1}H-NMR (60 MHz, CDCl$_3$): 5.3 (*s*, (br.), NH$_2$); 4.65 (*s*, CH$_2$). ^{13}C-NMR (25 MHz, CDCl$_3$): 154.9 (*s*, CO); 121.8 (*q*, *J*(F,C) = 284, C(3)); 81.5 (*q*, *J*(F,C) = 35, C(2)); 67.0 (*s*, C(1)).

8. *General Procedure for the Synthesis of α-Substituted 2,2-Dichloro-3,3,3-trifluoropropanols.* By replacing paraformaldehyde by other aliphatic or aromatic aldehydes, the procedure for the preparation of **1** can be followed for the synthesis of a wide variety of α-substituted 2,2-dichloro-3,3,3-trifluoropropanols.

8.1. *2,2-Dichloro-1,1,1-trifluoro-4-methyl-3-pentanol* (**11**). From 2-methylpropionaldehyde after 2 d at r.t., **11** was isolated as a colourless oil in 80% yield. B.p. 55–60°/20 Torr. IR (neat): 3480*m* (br.), 2960*m*, 2930*w*, 2880*w*, 1470*w*, 1395*w*, 1290*w*, 1255*s*, 1200*s* (br.), 1020*m*, 1000*w*, 920*m*, 870*s*, 702*s*. ^{1}H-NMR (60 MHz, CDCl$_3$): 4.07 (*d*, *J* = 3, H–C(3)); 2.9 (br. *s*, O*H*); 2.4 (*m*, H–C(4)); 1.1 (2*d*, *J* = 7 each, 2 CH$_3$).

8.2. *4,4-Dichloro-5,5,5-trifluoro-1-penten-3-ol* (**12**). From acrolein after 2 d at r.t., **12** was isolated as a colourless oil in 60% yield. B.p. 70°/22 Torr. IR (neat): 3400*m* (br.), 1430*w*, 1380*w*, 1255*s*, 1200*s* (br.), 1140*m*, 1060*m* (br.), 990*m*, 945*s*, 930*s*, 870*s*, 855 (sh), 720*s*. ^{1}H-NMR (60 MHz, CDCl$_3$): 6.4–5.3 (*m*, 3 olefin, H); 4.7 (*d*, *J* = 6, H–C(3)); 3.3 (br. *s*, OH). ^{19}F-NMR (94 MHz, CDCl$_3$): −75.5 (*s*).

8.3. *2,2-Dichloro-1,1,1-trifluoro-5-methyl-4-hexen-3-ol* (**13**). From *β,β*-dimethylacrolein after 1 d at r.t., **13** was isolated as a colourless oil in 63% yield. B.p. 90–91°/39 Torr. ^{1}H-NMR (250 MHz, CDCl$_3$): 5.40 (*d*, *J* = 7.5, H–C(4)); 4.85 (*dd*, *J* = 7.5, 7.5, H–C(3)); 2.18 (*d*, *J* = 7.5, OH); 1.86 (2*d*, *J* = 2 each, 2 CH$_3$). ^{13}C-NMR (25 MHz, CDCl$_3$): 141.9 (*s*, C(5)); 122.1 (*q*, *J*(F,C) = 284, C(1)); 119.6 (*s*, C(4)); 88.2 (*q*, *J*(F,C) = 31, C(2)); 72.3 (*s*, C(3)); 26.0, 18.8 (2*s*, 2 CH$_3$).

8.4. *(E)-4,4-Dichloro-5,5,5-trifluoro-1-phenyl-1-penten-3-ol* (**14**). From (*E*)-cinnamaldehyde after 3.5 h at r.t., **14** was isolated as a pale yellow oil in 69% yield. B.p. 99–100°/0.05 Torr. ^{1}H-NMR (250 MHz, CDCl$_3$): 7.48–7.26 (*m*, 5 arom. H); 6.48 (*d*, *J* = 16, H–C(1)); 6.35 (*dd*, *J* = 6, 16, H–C(4)); 4.83 (*dd*, *J* = 6, 7, H–C(3)); 2.49 (*d*, *J* = 7, OH). ^{13}C-NMR (25 MHz, CDCl$_3$): 136.6 (*s*); 135.6 (*s*); 128.8 (*s*); 127.0 (*s*); 122.8 (*s*); 122.1 (*q*, *J*(F,C) = 284, C(5)); 87.5 (*q*, *J*(F,C) = 32, C(4)); 76.7 (*s*, C(3)). ^{19}F-NMR (94 MHz, CDCl$_3$): −74.8 (*s*).

8.5. *2,2-Dichloro-3,3,3-trifluoro-1-phenylpropan-1-ol* (**15**). From benzaldehyde after 1 d at r.t., **15** was isolated as a colourless oil in 95% yield. B.p. 66°/0.01 Torr. ^{1}H-NMR (250 MHz, CDCl$_3$): 7.56–7.32 (*m*, 5 arom. H); 5.26 (br. *s*, H–C(1)); 2.85 (br. *s*, OH). ^{13}C-NMR (25 MHz, CDCl$_3$): 135.7 (*s*); 129.6 (*s*); 128.8 (*s*); 128.1 (*s*); 122.3 (*q*, *J*(F,C) = 284, C(3)); 87.6 (*q*, *J*(F,C) = 32, C(2)); 77.3 (*s*, C(1)). ^{19}F-NMR (94 MHz, C$_6$D$_6$): −74.1 (*s*). Anal. calc. for $C_9H_7Cl_2F_3O$ (259.05): C 41.73, H 2.72, Cl 27.37, F 22.00; found: C 42.03, H 2.88, Cl 26.14, F 21.92.

8.6. *2,2-Dichloro-3,3,3-trifluoro-1-(2-furyl)propan-1-ol* (**16**). From furane-2-carbaldehyde after 3 d at r.t., **16** was isolated as a yellow oil in 98% yield. B. p. 94–95°/28 Torr. ^{1}H-NMR (60 MHz, CDCl$_3$): 7.5 (*m*, 1 arom. H); 6.5 (*m*, 2 arom. H); 5.3 (*s* (br.), H–C(1)); 3.05 (br. *s*, OH).

REFERENCES

[1] 'Biomedicinal Aspects of Fluorine Chemistry', Eds. R. Filler and Y. Kobayashi, Elsevier Biomedical Press, Amsterdam, 1982.

[2] 'Organofluorine Chemicals and their Industrial Applications', Ed. R.E. Banks, Ellis Horwood Ltd., Chichester, 1979.

[3] *Imperial Chemical Industries*, Fr. Pat. 1496633 (prior. 14.10.1966) (*Chem. Abstr.* **1968,** *69,* 51584a).

[4] A. Posta, O. Paleta, *Collect. Czech. Chem. Commun.* **1972,** *37,* 3946.

[5] A.H. Fainberg, M. Hauptschein *(Pennsalt Chemicals Corp.),* US Pat. 3290333 (prior. 9.9.1963) (*Chem. Abstr.* **1966,** *66,* 65633r).

[6] *Anon.* UK, Res. Discl. **1982,** *219,* 239 (*Chem. Abstr.* **1983,** *98,* 16322r).

[7] I. Hemer, A. Posta, V. Dedek, *J. Fluorine Chem.* **1985,** *29,* 86.

[8] T. Kitazume, N. Ishikawa, *J. Am. Chem. Soc.* **1985,** *107,* 5186.

[9] T. Kitazume, N. Ishikawa, *Chem. Lett.* **1981,** 1679.

[10] R.W. Lang *(Ciba-Geigy AG),* Eur. Pat. appl. 157739 (prior. 29.3.1984).

[11] L.F. Fieser, M. Fieser, 'Reagents for Organic Synthesis', J. Wiley & Sons, New York, 1967, p. 1276.

[12] W.C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978,** *43,* 2923.

[13] R.N. Haszeldine, *J. Chem. Soc.* **1951,** 2495.