ELSEVIER

Journal of Fluorine Chemistry, 76 (1996) 15–19

JOURNAL OF FLUORINE CHEMISTRY

Fluorination of 2-oxo-ethane derivatives with diethylaminosulfur trifluoride (DAST)

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Received 2 September 1994; accepted 22 August 1995

Abstract

The fluorination of 2-oxo-ethane derivatives with DAST is described. The use of ZnI_2 as a catalyst improves the yield in the fluorination of 2-phenyl-2-oxo-acetonitrile with DAST.

Keywords: Diethylaminosulfur trifluoride; Difluoromethylene compounds; ZnI_2 catalyst; NMR spectroscopy; 2-Oxo-ethane derivatives

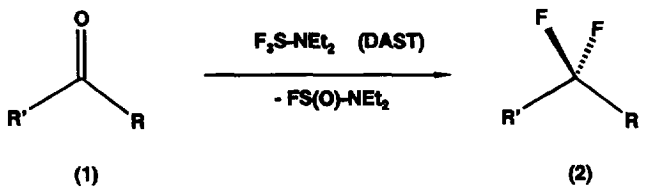
1. Introduction

Diethylaminosulfur trifluoride is a widely used and effective fluorinating agent. It has been predominantly applied to convert alcohols, aldehydes, ketones and glyoxalates into the corresponding monofluoromethyl and difluoromethylene derivatives [1–5]. Less common is the conversion of dialkyl sulfoxides to fluorinated thioethers [6,7], or of cyanohydrins to fluorocyanides [8]. In addition, DAST has been applied to induce rearrangement reactions [9,10]. Furthermore, DAST plays an important role in the synthesis of fluorinated derivatives of natural products, e.g. fluorinated steroids [11], sugars [12], nucleosides and nucleotides [13], and amino acids [14].

2. Results and discussion

We wish to report on the synthesis of several 2-aryl- and 2-alkyl-2,2-difluoroethane derivatives, which might be useful as building blocks for potentially biorelevant organofluorine compounds. Thus, the carbonyl compounds **1** are converted to difluoromethylene derivatives **2** as shown in Scheme 1.

In principle, this reaction was studied in detail by Middleton as early as 1975 [2], but attracted our attention very recently in connection with our studies on C-fluorinated organophosphorus compounds. When R represents hydrogen or functional groups such as carboxylate or nitrile, this reaction leads conveniently to difluorinated toluenes, difluorinated arylacetic acid esters and difluorinated nitriles [15].



(1) (2)

R = COOEt, CH(OEt)$_2$, CN; R, R' = Alkyl, Aryl.

Scheme 1.

Middleton and Bingham [5] in 1980 described the synthesis of several 2-aryl-2,2-difluoroacetic acid esters according to Scheme 1, using 2 equiv. of DAST per 1 equiv. of 2-aryl-2-oxo-acetic acid ester. We re-investigated the reaction of 2-phenyl-, 2-(4-fluorophenyl)- and 2-(3-trifluoromethylphenyl)-2-oxo-acetic acid ethyl esters **2a–c** with DAST according to Scheme 2a.

We found that 1 equiv. of DAST is sufficient to convert 1 equiv. of 2-aryl-2-oxo-acetic acid esters, provided that after the initial exothermic phase the reaction mixture is heated for 4 h at 60 °C and then left at room temperature overnight. The 2-aryl-2,2-difluoroacetic acid esters are obtained in good yield as listed in Table 1. Middleton used $CFCl_3$ as an extractant during the aqueous work-up procedure for the reaction mixture. It is adequate to replace $CFCl_3$, an ozone layer damaging fluorochlorocarbon, by CH_2Cl_2. Yields were not reduced when the strongly acidic aqueous phase was neutralised with solid $NaHCO_3$ before extraction with CH_2Cl_2.

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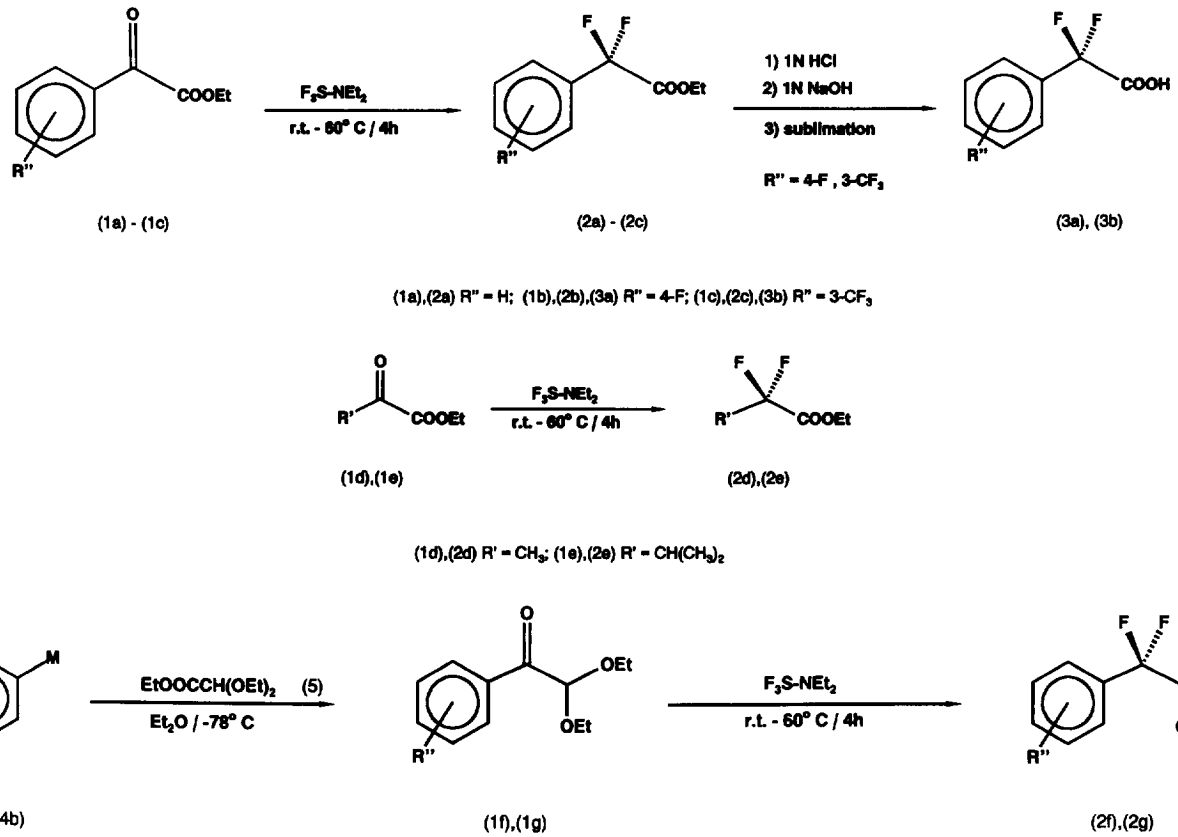
[1] Part of a forthcoming Ph.D thesis.

SSDI 0022-1139(95)03346-7



Scheme 2.

The esters **2b** and **2c** were hydrolysed with 1 N NaOH and the resulting reaction mixtures treated with dilute hydrochloric acid [5] (see Scheme 2a). We obtained the 2-aryl-2,2-difluoroacetic acids **3a** and **3b** as yellow oils which partly crystallised upon cooling to 8 °C. Recrystallisation from non-polar solvents like hexane, pentane or ligroin failed. Instead, sublimation of the crude solid/oil mixtures in vacuo afforded the acids **3a** and **3b** as hygroscopic, white, crystalline products as shown in Table 1.

The same fluorination procedure was successfully extended to 2-alkyl-2-oxo-ethane derivatives according to Scheme 2b.

This led to good yields of 2,2-difluoropropionic and isobutyric acid derivatives as shown in Table 1.

2-Phenyl-2,2-difluoroacetaldehyde was synthesised in 1990 by Suga and Schlosser [16] via a multistep procedure including a Pummerer reaction. It is reported to be an unstable product which decomposes rapidly at room temperature. In

Table 1
Novel syntheses of R′–CF_2–R (**2a–h**) by fluorination of R′–CO–R (**1**) with DAST

Compound	R′	R	Yield (%)	b.p. (°C/[torr]), m.p. (°C), subl. (°C/[torr])
2a	C_6H_5	COOEt	75.6	100 [20]
2b	4-F-C_6H_4	COOEt	77.5	83 [0.3]
2c	3-CF_3-C_6H_4	COOEt	7.9	103 [20]
2d	CH_3	COOEt	62.3	33–34 [30]
2e	$(CH_3)_2CH$	COOEt	60.1	55 [20]
2f	C_6H_5	$CH(OEt)_2$	79.4	93 [0.3]
2g	4-F-C_6H_4	$CH(OEt)_2$	77.5	91 [0.3]
2h	C_6H_5	CN	65.3	86 [80]
3a	4-F-C_6H_4	COOH	76.7	51 (m.p.), 70 °C [0.001]
3b	3-CF_3-C_6H_4	COOH	85.5	40 (m.p.), 70 °C [0.001]

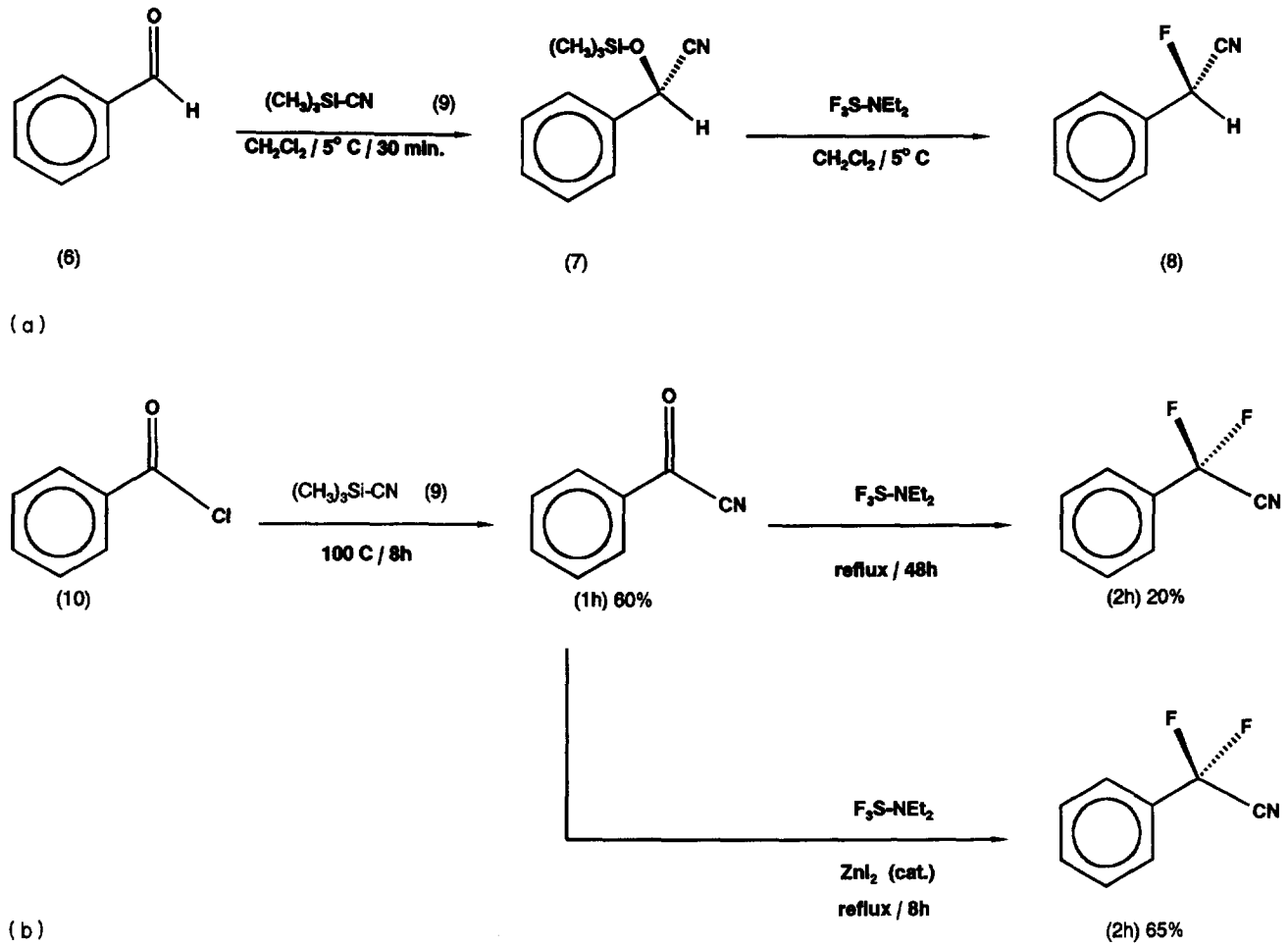
order to avoid this multistep procedure we sought 2-aryl-2-oxo-acetaldehyde derivatives which could be easily converted into 2-aryl-2,2-difluoroacetaldehyde derivatives by Middleton's method. We found that the 2-aryl-2-oxo-acetaldehyde diethylacetals **1f** and **1g** are accessible via the Grignard method or the reaction of the aryllithium compounds **4a** and **4b** with 2,2-diethoxyacetic acid ethyl ester (**5**) at low temperature and react with DAST to yield the 2-aryl-2,2-difluoroacetaldehyde ethylacetals **2f** and **2g** as shown in Scheme 2c.

Since these acetals are stable at room temperature for several months and can be distilled without decomposition, they may serve as a convenient storage form of the unstable 2-aryl-2,2-difluoroacetaldehydes.

All attempts to cleave the 2-aryl-2,2-difluoroacetaldehyde diethylacetals to the free aldehydes with formic acid, trifluoroacetic acid, bromotrimethylsilane and iodotrimethylsilane [17] failed. At ambient temperature and after 1 h to 2 d, only unreacted starting materials were recovered in nearly quantitative yield, as shown by NMR spectroscopy. Strongly acidic conditions and high temperatures resulted in complete decomposition of the 2-aryl-2,2-difluoroacetaldehyde diethylacetals. Further investigations on the cleavage of 2,2-difluorinated aldehyde acetals will be carried out.

The easy and convenient conversion of the aldehydes to the 2-monofluoroacetonitrile **8** with trimethylsilyl cyanide (**9**), (TMSCN) [8] and DAST according to Scheme 3a, and the recently reported two-step procedure [15] obtain 2-aryl-2,2-difluoroacetonitriles **2h** [5] prompted us to investigate the reaction of aromatic acyl chlorides **10** with TMSCN (**9**) and DAST according to Scheme 3b.

Thus, benzoyl chloride (**10**) was refluxed for 8 h with TMSCN (**9**) to yield 2-phenyl-2-oxo-acetonitrile (**1h**), which was not isolated but directly reacted with DAST at reflux temperature for another 8 h. In our hands, this reaction yielded only small amounts of 2-phenyl-2,2-difluoroacetonitrile (**2h**) (12% total yield) even when 2 equiv. of DAST were used and reaction times were increased up to 48 h. In the literature [7] we found several examples that Lewis acids enhance the fluorination power of DAST in cases of less reactive substrates. In our case, we obtained the best results using ZnI_2. By addition of catalytic amounts of ZnI_2 we were able to increase the yield in the reaction of 2-phenyl-2-oxo acetonitrile (**1h**) with DAST to 65% whereas other Lewis



Scheme 3.

acids, e.g. $AlCl_3$ or $SbCl_3$, had no influence on the yield. All results are summarised in Table 1. The 2-oxo-ethane derivatives **2**, used as precursors, were synthesised by well-known standard procedures [18,19].

3. Experimental details

DAST was purchased from Th. Schuchardt & Merck, Darmstadt, Germany. Educts **1a–h** were synthesised according to literature methods [18,19]. NMR samples were prepared as ca. 5% (^{19}F) and 10% (^{1}H) solutions in $CDCl_3$. Acids were measured as 10% solutions in 1 M $DClO_4$ ($HClO_4$ in D_2O). Internal references: TMS and C_6F_6. NMR spectra were recorded on a Bruker AM 200SY spectrometer. The standard sign convention for chemical shifts is used: positive resonance sequences correspond to positive chemical shifts.

*3.1. Fluorination of 2-aryl-2-oxo-ethane derivatives **1a–g** with DAST. General procedure for the synthesis of compounds **2a–g***

A 100 ml Teflon flask fitted with a reflux condenser and a 10 ml dropping funnel (ordinary laboratory glass) was carefully dried and saturated with nitrogen. In the Teflon flask were placed 46 mmol of the corresponding 2-aryl- or 2-alkyl-2-oxo-ethane derivative. Via the dropping funnel, 46 mmol of DAST (7.41 g, 6.1 ml) were added dropwise. In the case of 2-aryl- and 2-alkyl-2-oxo-acetic acid esters **1a–e** the temperature increased to 55 °C, whereas no exothermic effect was observed in the fluorination of acetals **1f** and **1g**. After cooling to room temperature, the reaction mixture was heated for 4 h to 60 °C. The reaction mixture was then poured into 200 ml of ice-water. After the addition of 100 ml of CH_2Cl_2, the organic and the aqueous phase were separated. The organic phase was subsequently washed with 50 ml of saturated aq. $NaHCO_3$ and three times with 50 ml of saturated aq. NaCl solution. The aqueous phase was neutralised with solid $NaHCO_3$ and extracted three times with 50 ml of CH_2Cl_2. The CH_2Cl_2 phases were washed with 50 ml of saturated NaCl solution. The combined organic phases were dried over Na_2SO_4. Evaporation of the solvent afforded light yellow oils which were distilled in vacuo.

2-Phenyl-2,2-difluoroacetic acid ethyl ester (**2a**): Yield, 75.6%; b.p. 100 °C/20 Torr. ^{1}H NMR (10% $CDCl_3$/TMS) δ: 7.64–7.59 (2H arom., m); 7.48–7.44 (3H arom., m); 4.28 (2H, q., $^{3}J_{HH}$ = 7.1 Hz); 1.29 (3H, t., $^{3}J_{HH}$ = 7.1 Hz) ppm. ^{19}F NMR (5% $CDCl_3/C_6F_6$) δ: 57.97 (s) ppm. Analysis: Calc. for $C_{10}H_{10}F_2O_2$: C, 59.98; H, 5.04%. Found: C, 59.95; H, 5.00%.

2-(4-Fluorophenyl)-2,2-difluoroacetic acid ethyl ester (**2b**): Yield, 77.5%; b.p. 83 °C/0.3 Torr. ^{1}H NMR (10% $CDCl_3$/TMS) δ: 7.71–7.66 (2H arom., m.); 7.23–7.14 (2H arom., m.); 4.33 (2H, q., $^{3}J_{HH}$ = 7.2 Hz); 1.31 (3H, t., $^{3}J_{HH}$ = 7.2 Hz) ppm. ^{19}F NMR (5% $CDCl_3/C_6F_6$) δ: 58.81 (2F, s.); 52.81 (1F, m.) ppm. Analysis: Calc. for $C_{10}H_9F_3O_2$: C, 55.03; H, 4.16%. Found: C, 55.10; H, 4.12%.

2-(3-Trifluoromethylphenyl)-2,2-difluoroacetic acid ethyl ester (**2c**): Yield, 72.9%; b.p. 103 °C/0.3 Torr. ^{1}H NMR (10% $CDCl_3$/TMS) δ: 7.89–7.57 (4H arom., m.); 4.32 (2H, q., $^{3}J_{HH}$ = 7.1 Hz); 1.32 (3H, t., $^{3}J_{HH}$ = 7.1 Hz) ppm. ^{19}F NMR (5% $CDCl_3/C_6F_6$) δ: 98.97 (3F, s.), 57.76 (2F, s.) ppm. Analysis: Calc. for $C_{11}H_9F_5O_2$: C, 49.24; H, 3.38%. Found: C, 49.35; H, 3.40%.

2,2-Difluoropropanoic acid ethyl ester (**2d**): Yield, 62.3%, b.p. 33–34 °C/30 Torr. ^{1}H NMR (10% $CDCl_3$/TMS) δ: 4.26 (2H, q., $^{3}J_{HH}$ = 7.2 Hz); 1.74 (3H, t., $^{3}J_{FH}$ = 18.8 Hz); 1.29 (3H, t., $^{3}J_{HH}$ = 7.2 Hz) ppm. ^{19}F NMR (5% $CDCl_3/C_6F_6$) δ: 62.72 (2F, q., $^{3}J_{FH}$ = 18.8 Hz) ppm. Analysis: Calc. for $C_5H_8F_2O_2$: C, 43.46; H, 5.84%. Found: C, 43.55; H, 5.90%.

2,2-Difluoro-3-methylbutanoic acid ethyl ester (**2e**): Yield, 60.1%; b,p. 55 °C/20 Torr. ^{1}H NMR (10% $CDCl_3$/TMS) δ: 4.25 (2H, q., $^{3}J_{HH}$ = 7.2 Hz); 2.29 (1H, m., $^{3}J_{HH}$ = 7.2 Hz, $^{3}J_{FH}$ = 14.47 Hz); 1.28 (3H, t., $^{3}J_{HH}$ = 7.2 Hz); 0.97 (6H, d., $^{3}J_{HH}$ = 7.2 Hz) ppm. ^{19}F NMR (5% $CDCl_3/C_6F_6$) δ: 47.29 (2F, d., $^{3}J_{FH}$ = 14.74 Hz) ppm. Analysis: Calc. for $C_7H_{12}F_2O_2$: C, 50.58; H, 7.28%. Found: C, 50.60; H, 7.24%.

2-Phenyl-2,2-difluoroacetaldehyde diethylacetal (**2f**): Yield, 79.4%; b.p. 93 °C/0.3 Torr. ^{1}H NMR (10% $CDCl_3$/TMS) δ: 7.60–7.34 (5H arom., m.); 4.65 (t., 1H, $^{3}J_{FH}$ = 4.7 Hz); 3.85–3.55 (4H, m., $^{2}J_{HH}$ = −9.3 Hz, $^{3}J_{HH}$ = 7.1 Hz); 1.22 (6H, $^{3}J_{HH}$ = 7.1 Hz) ppm. ^{19}F NMR (5% $CDCl_3/C_6F_6$) δ: 54.94 [m. (broad, indicating hindered rotation)] ppm. Analysis: Calc. for $C_{12}H_{16}F_2O_2$: C, 62.60; H, 7.00%. Found: C, 63.00; H, 7.12%.

2-(4-Fluorophenyl)-2,2-difluoroacetaldehyde diethylacetal (**2g**): Yield, 77.5%; b.p. 91 °C/0.3 Torr. ^{1}H NMR (10% $CDCl_3$/TMS) δ: 7.56–7.49 (2H, m.); 7.25–7.03 (2H, m.); 4.65 (1H, t., $^{3}J_{FH}$ = 4.7 Hz); 3.84–3.61 (4H, m., $^{2}J_{HH}$ = −9.4 Hz, $^{3}J_{HH}$ = 7.0 Hz); 1.22 (6H, t., $^{3}J_{HH}$ = 7.0 Hz) ppm. ^{19}F NMR (5% $CDCl_3/C_6F_6$) δ: 55.30 (broad, indicating hindered rotation), 2F, m.]; 50.44 (1F, m.) ppm. Analysis: Calc. for $C_{12}H_{15}F_3O_2$: C, 58.04; H, 6.09%. Found: C, 58.22; H, 6.07%.

*3.2. Hydrolysis of 2-aryl-2,2-difluoroacetic acid ethyl esters **2b and 2c***

*Synthesis of 2-aryl-2,2-difluoroacetic acids **3a and 3b** [5]*

2-Aryl-2,2-difluoroacetic ethyl ester (27 mmol) was mixed with 37 ml of 1 N NaOH and stirred for 24 h at room temperature. After the addition of 37 ml of 1 N HCl, the aqueous phase was extracted three times with 100 ml of CH_2Cl_2. The organic phase was washed with 200 ml of saturated aq. NaCl solution and dried over Na_2SO_4. After evaporation of the solvent, the partly crystallised oil was sublimed in vacuo at 0.001 Torr and 70–80 °C.

2-(4-Fluorophenyl)-2,2-difluoroacetic acid (**3a**): Yield, 76.7%; subl. temp. 75 °C/0.001 Torr. ^{1}H NMR (10% $DClO_4$) δ: 7.66–7.757 (2H, m.); 7.31–7.16 (2H, m.) ppm.

^{19}F NMR (10% $DClO_4$) δ: 58.81 (2F, s.); 52.88–52.75 (1F, m.) ppm. Analysis: Calc. for $C_8H_6F_2O_2$: C, 55.80; H, 3.51%. Found: C, 55.53; H, 3.45%.

2-(3-Trifluoromethylphenyl)-2,2-difluoroacetic acid (**3b**): Yield, 71.2%; subl. temp. 79 °C/0.001 Torr. ^1H NMR (10% $DClO_4$) δ: 10.33 (1H, s., COOH); 7.89–7.58 (4H arom., m.) ppm. ^{19}F NMR (10% $DClO_4$) δ: 98.84 (3F, s.); 65.94 (2F, s.) ppm. Analysis: Calc. for $C_9H_5F_5O_2$: C, 45.02; H, 2.10%. Found: C, 44.95; H, 2.19%.

*Synthesis of 2-phenyl-2,2-difluoroacetonitrile (**2h**)*

Benzoic acid chloride (2.4 g, 19 mmol, 1.98 ml), 1.9 g (19 mmol, 2.5 ml) of cyanotrimethylsilane (TMSCN) [19] and 40 mg of ZnI_2 (catalyst) [19] were heated with exclusion of moisture for 8 h at 100 °C. After the solution had cooled down to room temperature, 20 mg of ZnI_2 and subsequently 6 g (37 mmol) of DAST were added at 5 °C (ice bath). When addition was complete, the reaction mixture was refluxed for another 8 h. The reaction mixture was poured into 200 ml of ice-water and extracted with 100 ml of CH_2Cl_2. After separation of the organic and aqueous phases, the aqueous phase was neutralised with solid $NaHCO_3$ and extracted three times with 50 ml of CH_2Cl_2. The organic phase was subsequently washed with saturated aq. $NaHCO_3$ and saturated aq. NaCl solutions and dried over Na_2SO_4. Evaporation of the solvent afforded an intensively yellow coloured liquid which was distilled in vacuo (80 Torr).

2-Phenyl-2,2-difluoroacetonitrile (**2h**): Yield, 65.3%; b.p. 86 °C/80 Torr. ^1H NMR (10% $CDCl_3$/TMS) δ: 8.20–8.13 (2H arom., m.); 7.84–7.75 (1H arom., m.); 7.69–7.57 (2H arom., m.) ppm. ^{19}F NMR (5% $CDCl_3/C_6F_6$) δ: 78.71 (s.) ppm. Analysis: Calc. for $C_8H_5F_2N$: C, 62.73; H, 3.29; N, 9.15%. Found: C, 62.78; H, 3.25; N, 9.09%.

Acknowledgement

This study was supported by the Fonds der Chemischen Industrie e. V. Thanks are due to the Deutsche Forschungsgemeinschaft and the Ministerium für Wissenschaft und Forschung NRW for supporting the Arbeitsgemeinschaft Fluorchemie Nordrhein Westfalen.

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