Synthesis of α,α-difluoronitriles from acyl cyanides*

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(Received March 4, 1992; accepted June 30, 1992)

Abstract

Aromatic α,α-difluoronitriles (aryl α,α-difluoroacetonitriles) have been synthesized by reaction of aroyl cyanides with diethylamino sulphur trifluoride. Some liquid crystalline difluoronitriles have been prepared by this method.

Introduction

The $-CF_2-CN$ group is a very polar, strongly electron-withdrawing substituent. Nevertheless, one would expect it to exhibit rather different properties than those found for non-fluorinated nitriles: as in other systems, fluorination should diminish the intermolecular interactions [1]. Several methods for the synthesis of difluoronitriles are described in the literature. Most frequently, these compounds are prepared by the standard nitrile synthesis starting from difluoro carboxylic esters or halides via reaction with ammonia and subsequent dehydration of the amides formed [see, for example, refs. 2 and 3]; since the starting compounds, if not commercially available, have to be prepared by preceding reactions, the entire preparation usually involves a multistep procedure. Further methods of synthesis have been described only for special cases, such as the addition of cyanide to a 1,1-difluoroethene derivative with trapping of the intermediate anion by an electrophile [4, 5], or the cyanidation of perfluoroalkyl Grignards with phenyl cyanate [6]. α,α-Difluoro-substituted benzyl cyanides can also be made from the parent benzyl cyanides by chlorination with SO_2Cl_2 and subsequent chlorine/fluorine exchange with SbF_3 [7], or directly by means of $FClO_3$ [8], or by electrochemical fluorination [9]. An interesting synthetic alternative would be the transformation of a carbonyl group adjacent to a cyano group into a difluoromethylene moiety, i.e. the fluorination of an acyl cyanide by means of fluorinating agent such as sulphur tetrafluoride or diethylamino sulphur trifluoride (DAST) [eqn. (1), A=CN].

*Dedicated to Professor Alois Haas on the occasion of his 60th birthday.
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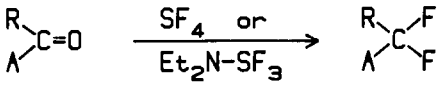
0022-1139/93/$6.00

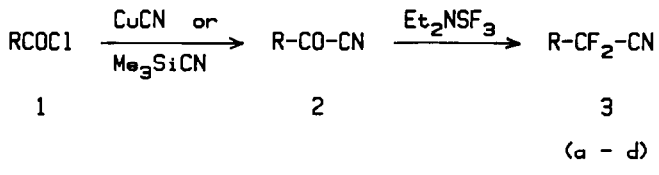


(1)

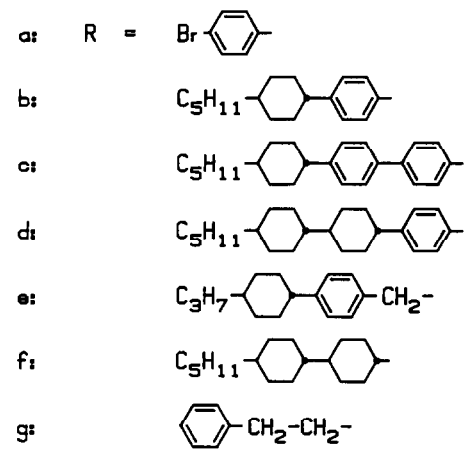
Generally, carbonyl fluorination has become a well-established method in synthetic chemistry [10–15], and with DAST it proceeds particularly easily if the carbonyl group is attached to an electron-withdrawing group (A = CO_2R', CF_3, CF_2R'') [3, 16]. However, the reaction apparently has not been investigated so far with cyanide as an adjacent group*.

Results and discussion

The acyl cyanides **2**, used as starting materials for the reaction proposed above, can be easily prepared by a variety of methods [18]; we have employed the reaction of acyl chlorides **1** with cuprous cyanide or trimethyl silyl cyanide [see eqn. (2)]. Their transformation into difluoronitriles **3** can indeed be carried out, at least in the case of aroyl cyanides [eqn. (2)].



(2)



Fluorination takes place by simple heating with DAST. However, in comparison to the analogous conversion of carbonyl groups activated by other electron-withdrawing groups, this reaction proceeds at a slower rate

*A similar reaction, the fluorination of cyanohydrins or of their silyl ethers with DAST giving monofluoronitriles, has been reported [17].

TABLE 1

Physical data for the liquid crystalline compounds **3(b–d)**[a]

	Phase range (°C)	A	B	C
3b	K 71	−110	11.6	8
3c	K 59 N (47.7) I	50	12.9	46
3d	K 76 SmB (74) N 81.5 I	60	13.3	37

[a]A = extrapolated clearing point (°C); B = dielectric anisotropy [1 kHz, 20 °C]; C = viscosity [20 °C] ($mm^2\ s^{-1}$); (A, B, C: extrapolated in LC-mixture Merck ZLI 1132). K: crystal; SmB: smectic B; N: nematic; I: isotropic liquid.

and the yields are only mediocre (see Experimental section)*†. Nevertheless, since the reactions can be carried out easily and the aroyl cyanides are readily available, this new reaction sequence can be considered a straightforward synthetic pathway for aromatic derivatives **3**, e.g. the new *p*-bromobenzene derivative **3a**. Because of our interest in the properties of liquid crystals containing fluorine [19], we have prepared, amongst others, the compounds **3(b–d)** [20]. The physical data with respect to their liquid crystalline behaviour are shown in Table 1. In comparison to non-fluorinated liquid crystalline nitriles, these new compounds are of comparable polarity of dielectric anisotropy; however, they show lower phase transition temperatures and also reduced viscosities.

Surprisingly, compounds **2(e–g)**, which contain the cyanocarbonyl group attached to an aliphatic moiety, did not react with DAST under the conditions used for the aromatic derivatives; normally, aliphatic carbonyl compounds are more reactive towards DAST than aromatic carbonyl compounds [12]. If more drastic conditions were used to enforce a reaction (80 °C, no solvent), other products were formed and the desired compounds could not be detected.

In conclusion, the reaction of aromatic acyl cyanides with DAST gives α,α-difluoronitriles in a simple manner, thus establishing an alternative synthetic route for this class of compounds.

Experimental

All starting materials and reagents were commercially available from Merck–Schuchardt, except the liquid crystalline acid chlorides **1(b–f)**, which were prepared according to methods described earlier [21–23]. The determination of the physical properties of the liquid crystalline compounds was performed as described elsewhere [19].

*The yields of **2** and **3** have not been optimized.

†Among the products of the reactions, the following could be identified by MS methods: the respective acyl fluoride, the dimer of the acyl cyanide [18] and a compound formed very likely by addition of the DAST molecule to the CN bond of **2** (not characterized further).

^{1}H NMR spectra were recorded at 200 MHz, ^{13}C NMR spectra at 50 MHz on a Brucker AC 200 spectrometer using TMS as an internal standard. Mass spectra were obtained with a Fisons VG 7070E mass spectrometer (70 eV electron energy).

All compounds having no cited reference are new.

Preparation of acyl cyanides ***2(a–f)***

A mixture consisting of 100 mmol of acyl chloride **1**, 13.4 g (150 mmol) copper(I) cyanide, 0.1 g phosphorus pentoxide and 60 ml toluene was refluxed for 40 h. After cooling to room temperature, the mixture was filtered, the filtrate washed with 10 ml of water and then concentrated *in vacuo*. After chromatography with toluene over a silica column, the eluate was evaporated *in vacuo* and the residue crystallized from hexane, in case of **2a** with cooling to −20 °C.

2-(4-Bromophenyl)-2-oxo-acetonitrile (**2a**) [24]: Yield: 50%; m.p., 65 °C (lit. value, 65–66 °C). ^{1}H NMR ($CDCl_3$) δ: 7.52 (d, 2H); 8.02 (d, 2H) ppm. MS *m/z*: 211; 209 (M^+); 185; 183 (100%); 157; 155.

2-Oxo-2-[4-(4-pentyl-cyclohexyl)phenyl]acetonitrile (**2b**): Yield: 64%; m.p., 37 °C. ^{1}H NMR ($CDCl_3$) δ: 0.85–1.6 (m, 16H); 1.91 (mc, 4H); 2.60 (tt, 1H); 7.43 (d, 2H); 8.07 (d, 2H) ppm. MS *m/z*: 283 (M^+, 100%).

2-Oxo-2-[4′-(4-pentyl-cyclohexyl)-[1,1′-biphenyl]-4-yl]acetonitrile (**2c**): Yield: 76%; m.p., 63 °C (liquid crystalline, clearing point above 200 °C). ^{1}H NMR ($CDCl_3$) δ: 0.85–1.65 (m, 16H); 1.8–2.05 (m, 4H); 2.57 (tt, 1H); 7.36 (d, 2H); 7.61 (d, 2H); 7.82 (d, 2H); 8.21 (d, 2H) ppm. MS *m/z*: 359 (M^+, 100%).

2-Oxo-2-[4-(4′-pentyl-[1,1′-bicyclohexyl]-4-yl)phenyl]acetonitrile (**2d**): Yield: 68%; m.p., 92 °C (liquid crystalline, clp. 172 °C). ^{1}H NMR ($CDCl_3$) δ: 0.75–2.05 (m, 30H); 2.58 (tt, 1H); 7.42 (d, 2H); 8.06 (d, 2H) ppm. MS *m/z*: 365 (M^+, 100%).

2-Oxo-3-[4-(4-propyl-cyclohexyl)phenyl]propiononitrile (**2e**): Yield: 73%; m.p., 127 °C. ^{1}H NMR ($CDCl_3$) δ: 0.91 (t, 3H); 1.0–1.55 (m, 9H); 1.75–2.0 (m, 4H); 2.53 (tt, 1H); 3.82 (s, 2H); 7.25 (mc, 4H) ppm. MS *m/z*: 269 (M^+); 242 (M − HCN, 100%); 215 (M − COCN).

2-Oxo-2-(4′-pentyl-[1,1′-bicyclohexyl]-4-yl)acetonitrile (**2f**): Yield: 45%; m.p., 90 °C. ^{1}H NMR ($CDCl_3$) δ: 0.7–1.6 (m, 22H); 1.7–1.95 (m. 8H); 2.36 (tt, 1H) ppm. MS *m/z*: 289 (M^+, vw); 263 (M − CN); 235 (M − COCN, 100%).

Preparation of ***2g***

A mixture consisting of 11.8 g (70 mmol) of 3-phenylpropionyl chloride, 10.0 g (104 mmol) trimethylsilyl cyanide and a trace of aluminium chloride was stirred at 100 °C for 24 h and then evaporated *in vacuo* at ambient temperature. The residue was distilled under reduced pressure (*c.* 100 mmHg), the product distilling off at 184–186 °C.

2-Oxo-4-phenyl-butyronitrile [25]: Yield: 59%. ^{1}H NMR ($CDCl_3$) δ: 2.99 (mc, 4H); 7.1–7.3 (m, 5H) ppm. MS *m/z*: 159 (M^+); 130; 105; 91 (100%).

Preparation of α,α-difluoronitriles 3(a–d)

A mixture consisting of 50 mmol acyl cyanide **2**, 15 ml (18.3 g, 112.5 mmol) DAST and 20 ml dichloromethane was refluxed for 24 h. The mixture was then diluted with an additional 20 ml dichloromethane and hydrolyzed (under cooling with ice) by slow addition of 10 ml water. The organic layer was separated and evaporated *in vacuo* and the residue was chromatographed with pentane over a short silica column. After evaporation of the eluate *in vacuo*, the residue was crystallized twice from ethanol (with **3b**: at −20 °C; the filtrates from crystallization yielded additional material by concentration and recrystallization); **3a** was crystallized twice from hexane at −70 °C.

2-(4-Bromophenyl)-2,2-difluoroacetonitrile (**3a**): m.p., 25 °C. ^{1}H NMR ($CDCl_3$) δ: 7.55 (d, 2H); 7.70 (d, 2H) ppm. MS *m/z*: 233; 231 (M^+, 100%).

2,2-Difluoro-2-[4-(4-pentyl-cyclohexyl)phenyl]acetonitrile (**3b**): Yield: 40%. ^{1}H NMR ($CDCl_3$) δ: 0.85–1.6 (m, 16H); 1.89 (mc, 4H); 2.54 (tt, 1H); 7.35 (d, 2H); 7.57 (d, 2H) ppm. ^{13}C NMR (^{1}H decoupled; $CDCl_3$ δ: 14.06; 22.69; 26.62; 32.19; 33.37; 34.05; 37.22; 37.28; 44.59; 109.07 (t, *J*(C–F) = 242.3 Hz); 112.69 (t, *J*(C–F) = 48.6 Hz); 125.23 (t, *J*(C–F) = 4.7 Hz); 127.68; 128.74 (t, *J*(C–F) = 25.2 Hz); 152.93 ppm. MS *m/z*: 305 (M^+, 100%).

2,2-Difluoro-2-[4′-(4-pentyl-cyclohexyl)-[1,1′-biphenyl]-4-yl]acetonitrile (**3c**): Yield 36%. ^{1}H NMR ($CDCl_3$) δ: 0.85–1.6 (m, 16H); 1.8–2.0 (m, 4H); 2.52 (tt, 1H); 7.30 (d, 2H); 7.51 (d, 2H); 7.72 (s, 4H) ppm. ^{13}C NMR (^{1}H decoupled; $CDCl_3$) δ: 14.06; 22.71; 26.67; 32.25; 33.50; 34.23; 37.29; 37.37; 44.24; 108.97 (t, *J*(C–F) = 242.6 Hz); 112.51 (t, *J*(C–F) = 48.2 Hz); 125.58 (t, *J*(C–F) = 4.7 Hz); 127.00; 127.46; 129.53 (t, *J*(C–F) = 25.3 Hz); 136.52; 145.37; 148.33 ppm. MS *m/z*: 381 (M^+, 100%).

2,2-Difluoro-2-[4-(4′-pentyl-[1,1′-bicyclohexyl]-4-yl)phenyl]acetonitrile (**3d**): Yield: 17%; ^{1}H NMR ($CDCl_3$) δ: 0.8–1.55 (m, 22H); 1.65–2.0 (m, 8H); 2.52 (tt, 1H); 7.34 (d, 2H); 7.57 (d, 2H) ppm. ^{13}C NMR (^{1}H decoupled; $CDCl_3$) δ: 14.08; 22.72; 26.71; 30.12; 30.17; 32.29; 33.63; 34.31; 37.50; 37.96; 42.83; 43.37; 44.62; 109.06 (t, *J*(C–F) = 242.3 Hz); 112.66 (t, *J*(C–F) = 48.5 Hz); 125.22 (t, *J*(C–F) = 4.7 Hz); 127.64; 128.74 (t, *J*(C–F) = 25.1 Hz); 152.89 ppm. MS *m/z*: 387 (M^+, 100%).

Acknowledgements

We thank Andreas Ruhl for carrying out the chemical syntheses, Dr Volker Eiermann for the preparation and interpretation of the NMR spectra, and Dr Ulrich Finkenzeller, Ray Jubb, Heike Prücher and Helga Schubert for measurements of the physical data of the liquid crystalline compounds.

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