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Difluoromethylation of some C–H acids with chlorodifluoromethane under conditions of phase transfer catalysis (PTC)

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ABSTRACT

Selected C–H acids react with difluorocarbene generated from chlorodifluoromethane with concentrated aqueous solution of sodium hydroxide, and a catalyst, benzyltriethylammonium chloride (TEBAC) in benzene or THF affording C-difluoromethyl substituted derivatives. This process is restricted to C–H acids of $pK_a \cong 16.3–19.1$. The observed facts are rationalized.

1. Introduction

There are at least two reasons for which fluorine atoms are introduced to organic compounds. First, they are isosteric with hydrogen ones, second – exhibit the highest electrophilicity from all elements (4.0 in Pauling's scale). Hence, difluoromethyl and trifluoromethyl groups significantly change physical and biological properties of organic compounds [1,2]. Difluoromethyl group is conveniently introduced by the reaction of organic anions with chlorodifluoromethane (freon R-22). We have previously shown that using freon R-22 in the presence of a concentrated aqueous solution of sodium hydroxide and a quaternary ammonium salt as a catalyst, in nonpolar aprotic solvent (phase transfer catalysis, PTC [3–6]), *N*-aryl amides are simultaneously *N*- and *O*-difluoromethylated [7], oximes *O*-difluoromethylated [7], while some nitrogen heterocycles, *N*-difluoromethylated [8].

2. Results and discussion

Now, we wish to report the results of our research on application of PTC to *C*-difluoromethylation of some C–H acids with freon R-22 (Scheme 1). According to literature, difluoromethylation of esters with freon R-22 was carried out in the presence of sodium or potassium *t*-butoxide [9,10–14], sodium hydride (usually in THF) [15,16–21], LDA [22–24], sodium hexamethyldisilylamide (NaHMDS) [11,25] or (*tris*-diethylamino)phosphine methylimide [26]. In the case of nitriles, sodium *t*-butoxide [9,10] or sodium hydride was applied. The C–H acids mentioned above possessed only one acidic hydrogen atom. Depending on the structure of esters or nitriles and reaction conditions, difluoromethylation occurred in yield from 19% to high.

For reaction of difluoromethylation we selected C–H acids listed in Table 1.

Taking into account that in the case of diphenylacetonitrile (**1a**) this process is fairly well described (it was carried out in the presence of two different bases) [9,10,15], our preliminary experiments were performed with **1a**. Passing the stream of freon R-22 into a vigorously stirred mixture of **1a**, 50% aq. sodium hydroxide, with benzyltriethylammonium chloride (TEBAC) as a catalyst, in benzene led to formation of (2-difluoromethyl)diphenylacetonitrile (**2a**) (Table 2, entry 1, Table 3).

The process requires rather extensive bubbling of freon R-22 to remove air from the reaction flask, otherwise **1a** is oxidized to benzophenone. Oxidation of 2-arylalkanenitrles (including **1a**) with oxygen under PTC conditions to the corresponding phenones is firmly established [27–29]. Reactions of **1a** carried out either in the presence of more diluted sodium hydroxide solutions or in different solvents and temperatures gave usually lower content of **2a** in the reaction mixtures (Table 2, entries 2–6). The reaction done in an aqueous–acetone solution of potassium hydroxide afforded particularly poor result (Table 2, entry 7). Previously, this combination of base and solvents was successfully applied for difluoromethylation of some nitrogen heterocycles [30]. Attempted difluoromethylation

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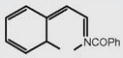
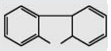
Table 1
C–H acids which were reacted with freon R-22.

1,2	a	b	c	d	e	f	g	h
R	Ph	Ph	Ph	Ph	Ph	PhS		Ph
X	Ph	2-$C_{10}H_7$	4-$O_2NC_6H_4$	NMe_2	Et	Et		CO_2Et
Y	CN	CN	CN	CN	CN	CN	CN	CO_2Et

1,2	i	j	k	l	m	n	o
R	$PhCH_2$	Me	Et	Ph	Ph	Ph	
X	CO_2Et	CO_2Et	CO_2Et	CN	Et	Bu	
Y	CO_2Et	CO_2Et	CO_2Et	CO_2Et	COPh	COPh	SMe

of other nitriles succeeded in the case of 1-naphtylphenylacetonitryle (**1b**) only, giving **2b** in a rather low yield (Table 3).

Pure **2a**,**b** were isolated by column chromatography in a low yield only, the majority of eluted fractions contained both **1a** and **2a** or **1b** and **2b**. This problem was solved by PTC alkylation of unreacted **1a**,**b** with isopropylchloroacetate, then separation of **2a**,**b** from alkylated **1a**,**b** by column chromatography (Table 3).

2-(4-Nitrophenyl)-(**1c**), (2-dimethylamino)phenylacetonitrile (**1d**), 2-phenyl- (**1e**) and (2-phenylsulfanyl)butyronitrile (**1f**) did not react with freon R-22, at all. Similarly, 2-benzoyl-1-cyano-1,2-dihydro-isoquinoline (**1g**, isoquinoline Reissert compound) proved inert.

Slightly different reactivity was observed in the case of substituted malonic esters **1h–k**. Diethyl phenylmalonate (**1h**) entered smooth reaction with freon R-22 (THF appeared a better solvent than benzene) forming **2h**, while alkyldiethylmalonates **1i–k** afforded the expected products **2i–k** in a lower yield, under harsher conditions (Table 3). On the other hand, neither (phenyl)ethylcyanoacetate (**1l**) nor 2-methylethylidenemalonate reacted with freon R-22. Reactions of esters **1h–k** were carried out in large excess of THF, otherwise their hydrolysis was noticed.

Finally we found that alkyl derivatives of desoxybenzoine **1m**,**n** and 9-methylsulfanylfluorene (**1o**) did not enter the reaction with freon R-22 under PTC conditions.

Table 2
Difluoromethylation of **1a** under different conditions.

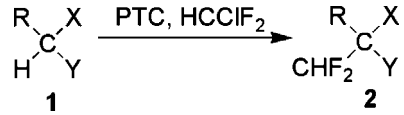
Entry	Base	Solvent	Temperature (°C)	Time (h)	Content of **2a** in reaction mixture[a] (%)
1	50% aq. NaOH	Benzene	20	6	62
2	50% aq. NaOH	Benzene	35–40	6	42
3	40% aq. NaOH	Benzene	20	7	61
4	30% aq. NaOH	Benzene	20	5.5	15
5	50% aq. NaOH	THF	20	6	49
6	50% aq. NaOH	Dioxane	20	3	14
7	40% aq. KOH	Acetone	40–50	8	6

[a] Determined by GC.

Table 3
Difluoromethylated C–H acids.

No.	Solvent	Temperature (°C)	Time (h)	Yield[a] (%)
2a	C_6H_6	20	6	43
2b	C_6H_6	20	6	12
2h	THF	20	1	64
2i	THF	50–60	11	40
2j	THF	20	5	36
2k	THF	50–60	9	7[b]

[a] Isolated, pure (≥98.5%) products.
[b] Determinated by GC. Identified by ^{1}H NMR.



Scheme 1. Difluoromethylation of C–H acids.

Different reactivity of C–H acids with freon R-22 seems depend on their acidities. Reported in literature p$K_{a(DMSO)}$ values of searched compounds are collected in Table 4 [31].

Under PTC conditions freon R-22 formed products with C–H acids of p$K_{a(DMSO)} \cong$ 16.3–19.1. Difluoromethylated C–H acids **2** resulted from reaction of difluorocarbene with carbanions and protonation of the difluoromethylanions thus formed. It means that both active particles, i.e., carbanions and difluorocarbene are generated under PTC conditions. According to Hine et al. [32,33] chlorodifluorocarbanion is not involved in alkaline hydrolysis of freon R-22. We found that it hydrolyzed (*via* difluorocarbene) when passed through a 50% aq. sodium hydroxide–benzene two-phase system, more efficiently when a PT catalyst was present. It seems that difluorocarbene formed difluoromethylanions with carbanions when they are formed in sufficiently high concentration (but under PTC conditions not exceeding that of a catalyst [3–6]) and exhibit high activity. Possibly, this is the case of C–H acids of pK_a = 16.3–19.1. C–H acids of p$K_a < 16$ fulfill the former condition but probably not the latter one. On the other hand, C–H acids of p$K_a > 19$ generate active carbanions but in concentration insufficiently high for reaction with difluorocarbene. We did not find measured pK_a for freon R-22, this value calculated from acidity coefficients [34] is ca 22. The results published by Hine et al. [32,33] mean that difluorocarbene from freon R-22 is generated at the interphase of two-phase system, particularly in the presence of C–H acids of p$K_a < 22$. Therefore, it seems that also at the interphase carbanions react with difluorocarbene. These considerations are rather simplified since we used pK_a values of C–H acids measured in DMSO [31], the conditions which only roughly resemble that of PTC. However, pK's of investigated C–H acids, measured in other solvents are scarcely available in literature.

We have demonstrated that PTC can be applied for difluoromethylation of C–H acids with freon R-22. The process is simple but restricted to C–H acids of p$K_a \cong$ 16.3–19.1. An explanation of observed facts is given.

Table 4
pK_a of C–H acids.

No.	pK_a (DMSO)
1a	17.5
1h	16.3
1j	18.7
1k	19.1
1l	8.0

3. Experimental

3.1. General

Melting points were measured on a capillary melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury spectrometer (at 400 and 100 MHz, respectively) in $CDCl_3$ with tetramethylsilane as external reference, chemical shifts are reported in ppm (δ = 0.00). The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Gas chromatography (GC) analyses were carried out on gas chromatograph Agilent 6850 Series GC System equipped with HP-50+ (30 m) column. Microanalyses were obtained using a CHN/S PerkinElmer 2400 element analyzer. Column chromatography was performed on Merck Kieselgel 60 (230–400 mesh) with hexane and ethyl acetate mixtures (gradient) as eluents. Chlorodifluoromethane, nitrile **1a**, malonates **1h–k** and 9-methylsulfanylfluorene (**1o**) were commercial, while nitriles **1b** [35], **1c** [36], **1d** [37], **1e** [38], **1f** [39], **1g** [40], (phenyl)ethylcyanoacetate (**1l**) [41] and desoxybenzoines **1m**,**n** [42] were prepared by literature procedures.

3.2. Procedure for preparation of 2a

Into three-necked round bottomed flask equipped with reflux condenser, mechanical stirrer, thermometer and glass pipe for introducing chlorodifluoromethane nitrile **1a** (0.97 g, 5 mmol), 50% aq. NaOH (1.20 g, 0.80 ml, 15 mmol), TEBAC (0.06 g, 0.25 mmol) and benzene (10 ml) were placed. The content of the flask was vigorously stirred and chlorodifluoromethane was bubbled through the mixture for 6 h (the progress of the reaction was monitored by GC). Then the mixture was diluted with water (10 ml), the water phase was extracted with benzene (3 × 5 ml), the organic extracts were dried over $MgSO_4$ and the solvent was evaporated. The residue (1.16 g) was dissolved in benzene (1 ml), cooled to 15 °C, 50% aq. NaOH (0.72 g, 0.48 ml, 9 mmol), TEBAC (0.005 g, 0.02 mmol) and isopropylchloroacetate (0.41 g, 3 mmol) were added. In atmosphere of argon, the mixture was vigorously stirred at temperature 10–20 °C for 0.5 h, then at 60–70 °C for 0.5 h, cooled and diluted with water (5 ml). The organic phase was separated, the water phase was extracted with benzene (3 × 5 ml), the organic extracts were washed with water (10 ml), dried over $MgSO_4$ and the solvent was evaporated. The product **2a** was isolated by column chromatography and crystallized (yield 43%).

2a, Solid, mp 84–85 °C, lit. [9] mp 85 °C, ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.43 (t, J = 54 Hz, 1H, CHF_2), 7.19–7.45 (m, 10H, ArH), ^{13}C NMR (50 MHz, $CDCl_3$): δ 56.44 (t, J = 20.5 Hz, **C**-CHF_2), 114.25 (t, J = 252 Hz, **C**HF_2), 117.70, 128.11, 128.27, 128.79, 128.92, 129.27, 130.16, 134.12, 140.30.

3.3. Procedure for preparation of 2b

Into three-necked, round bottomed flask equipped with reflux condenser, mechanical stirrer, thermometer and glass pipe for introducing chlorodifluoromethane, nitrile **1b** (0.97 g, 4 mmol), 50% aq. NaOH (0.96 g, 0.64 ml, 12 mmol), TEBAC (0.05 g, 0.2 mmol) and benzene (10 ml) were placed. The content of the flask was vigorously stirred and chlorodifluoromethane was bubbled through the mixture for 6 h at room conditions (the progress of the reaction was monitored by GC). The mixture was diluted with water (10 ml), the water phase was extracted with benzene (3 × 5 ml), the organic extracts were dried over $MgSO_4$ and the solvent was evaporated. The residue (1.02 g) was dissolved in benzene (2.5 ml), cooled to 15 °C, 50% aq. NaOH (1.84 g, 1.23 ml, 23 mmol), TEBAC (0.012 g, 0.05 mmol) and isopropylchloroacetate (0.96 g, 7 mmol) were added and the reaction was vigorously stirred under atmosphere of argon at temperature 10–20 °C for 0.5 h and at 60–70 °C for 0.5 h, then cooled and diluted with water (5 ml). The reaction was worked up as described in Section 3.3, the product **2b** was isolated by column chromatography and crystallized (yield 12%).

2b, solid, mp 134–135 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.63 (t, J = 54 Hz, 1H, C**H**F_2), 7.31–7.98 (m, 12H, ArH), ^{13}C NMR (100 MHz, $CDCl_3$): δ 54.41, 114.19 (t, J = 252 Hz, CHF_2), 117.13, 124.59, 125.03, 125.36, 126.13, 126.76, 127.98, 128.77, 129.11, 129.17, 129.32, 129.89, 130.90, 133.54, 134.88. Anal. Calcd. for $C_{19}H_{13}F_2N$: C, 77.80, H, 4.47, N, 4.78. Found: C, 77.76, H, 4.46, N, 4.78.

3.4. General procedure for preparation of 2h–k

Into the three-necked, round bottomed flask equipped with reflux condenser, mechanical stirrer, thermometer and glass pipe for introducing chlorodifluoromethane, malonate **1h–k** (4 mmol), 50% aq. NaOH (0.96 g, 0.64 ml, 12 mmol), TEBAC (0.05 g, 0.20 mmol) and THF (35 ml) were placed. The content of the flask was vigorously stirred and chlorodifluoromethane was bubbled through the mixture at the temperature and the time indicated in Table 3. After every 1.5 h, further portions of 50% aq. NaOH (0.96 g, 0.64 ml) were added. The progress of the reaction was monitored by GC. The mixture was diluted with CH_2Cl_2 (35 ml), the organic phase was decanted from the semisolid inorganic one which stuck to the wall of the flask, filtered through filter, and dried over $MgSO_4$. The solvent was evaporated, and the products **2h–j** were isolated by column chromatography in yields 36–64% (Table 3).

Reactions of nitriles **1c–g** with chlorodifluoromethane were carried out using Section 3.3 while C–H acids **1l–o** using Section 3.4.

2h, colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (t, J = 7.2 Hz, 6H, 2 × CH_3), 4.30–4.41 (m, 4H, 2 × CH_2), 6.56 (t, J = 55 Hz, 1H, C**H**F_2), 7.35–7.41 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.80, 62.57, 67.26 (t, J = 21.3, **C**-CHF_2), 114.03 (t, J = 247 Hz, **C**HF_2), 128.12, 128.58, 129.34, 130.24, 165.99, ^{19}F NMR (376 MHz, $CDCl_3$): δ −128.28 (d, J = 55 Hz, 2F).

2i, colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (t, J = 7 Hz, 6H, 2 × CH_3), 3.44 (s, 2H, CH_2), 4.17–4.30 (m, 4H, 2 × CH_2), 6.05 (t, J = 54 Hz, 1H, C**H**F_2), 7.18–7.28 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.82, 35.91, 62.14, 62.15, 114.37 (t, J = 247 Hz, **C**HF_2), 127.40, 128.42, 130.12, 134.22, 166.38. ^{19}F NMR (376 MHz, $CDCl_3$): δ −131.76 (d, J = 54 Hz, 2F). Anal. Calcd. for $C_{15}H_{18}F_2O_4$: C, 59.99, H, 6.04. Found: C, 59.88, H, 5.91.

2j, colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, J = 7.2 Hz, 6H, 2 × CH_3), 1.52 (s, 3H, CH_3), 4.23 (q, J = 7.2 Hz, 4H, 2 × CH_2), 6.34 (t, J = 55 Hz, 1H, C**H**F_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.03, 13.84, 58.13 (t, J = 22.8, **C**-CHF_2), 62.25, 114.46 (t, J = 245 Hz, **C**HF_2), 166.91. ^{19}F NMR (376 MHz, $CDCl_3$): δ −132.97 (d, J = 55 Hz, 2F).

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