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IMPROVEMENT OF THE SYNTHESIS OF ARYL DIFLUOROMETHYL ETHERS AND THIOETHERS BY USING A SOLID-LIQUID PHASE-TRANSFER TECHNIQUE

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SUMMARY

A new solid-liquid phase-transfer technique has been used to synthesize aryl difluoromethyl ethers and thioethers. Phenols (or thiophenols) and chlorodifluoromethane, dissolved in a cheap aprotic solvent of low polarity, are contacted with solid sodium hydroxide in the presence of a catalytic amount of tris-(3,6-dioxaheptyl)amine. The work-up of the reaction mixtures is very simple. Although yields are similar in both homogeneous and heterogeneous procedures using phenols, improved yields are obtained for thiophenols when using phase-transfer conditions.

INTRODUCTION

The last ten years have seen a rapid growth in the number of biologically active compounds, such as pesticides or drugs, based on aryl trifluoromethyl ethers and thioethers. The unique character of the CF_3O and CF_3S substituents, which are "superhalogens" (σ_I= +0.50, σ_R= −0.13 to −0.23 for CF_3O) [1]

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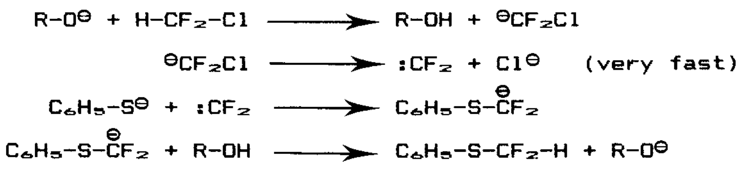
and lipophilic groups (π_R = 1.44 (CF_3S) and 1.04 (CF_3O) [2,3]) inert to strong acids, bases, oxidizers and reducers, explains the high activities and selectivities observed.

Recently, a new class of biologically active compounds (mainly pesticides) based on aryl difluoromethyl ethers and thioethers has appeared. The difluoromethoxy and difluoromethylthio groups are less electron-withdrawing, less lipophilic (π_R = 0.68 (CHF_2S) and 0.58 (CHF_2O) [2,3]), and less stable to strong acids than their trifluoro analogs, but these characteristics can be an advantage when particular selectivities or short-lived metabolites are required.

RESULTS AND DISCUSSION

Phenyl difluoromethyl thioethers were obtained for the first time by Hine et al. [4], who demonstrated that the thiophenate anion, though very nucleophilic, reacts very slowly with chlorodifluoromethane in methanol. However, when a stoichiometric amount of sodium methylate is present, the reaction between C_6H_5SNa and CHF_2Cl becomes 60 times faster and leads only to difluoromethylation of the thiophenate. This was one of the first demonstrations of the existence of difluorocarbene. The following mechanism was proposed:



$$R\text{-}O^{\ominus} + H\text{-}CF_2\text{-}Cl \longrightarrow R\text{-}OH + {}^{\ominus}CF_2Cl$$

$${}^{\ominus}CF_2Cl \longrightarrow :CF_2 + Cl^{\ominus} \quad \text{(very fast)}$$

$$C_6H_5\text{-}S^{\ominus} + :CF_2 \longrightarrow C_6H_5\text{-}S\text{-}\overset{\ominus}{C}F_2$$

$$C_6H_5\text{-}S\text{-}\overset{\ominus}{C}F_2 + R\text{-}OH \longrightarrow C_6H_5\text{-}S\text{-}CF_2\text{-}H + R\text{-}O^{\ominus}$$

Later, Miller and Thanassi [5] proposed a simpler method for the synthesis of aryl difluoromethyl ethers which was adapted by de Cat et al. [6] for the manufacture of aryl difluoromethyl thioethers:

$$\underset{(A=O,S)}{Ar\text{-}A\text{-}H} + CHF_2Cl + NaOH \xrightarrow[70^\circ C]{H_2O/dioxane} Ar\text{-}A\text{-}CF_2H + NaCl + H_2O$$

The mechanism is the same as that proposed by Hine (the difluorocarbene being generated by reaction of NaOH with chlorodifluoromethane) and, recently, has been proved unambiguously by deuterium exchange studies [7].

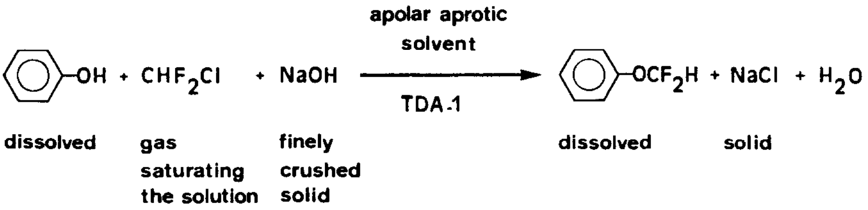
As a synthetic method, however, this technique suffers from several drawbacks:

- A high concentration of hydroxyl anions favours hydrolysis of the difluorocarbene.
- A rather high amount of aryl orthoformates is formed and might be related to a high concentration of phenate anions.
- Aryl difluoromethyl ethers and thioethers, especially when impure, are very sensitive to traces of aqueous acids and decompose autocatalytically. Hence, the work-up of the reaction medium becomes tedious, since washing with ion-exchanged water (pH= 6.5) is sufficient to partially decompose the product.
- Furthermore, dioxane is difficult to separate from water (and, in some cases, from the desired product) and to recycle.

For all these reasons, we decided to conduct the reaction between (thio)phenols, chlorodifluoromethane and sodium hydroxide in a two-phase solid-liquid system, finely crushed sodium hydroxide being the solid phase. We expected a sufficiently limited stationary concentration of anions to prevent the formation of by-products and hoped that the reaction would occur entirely under anhydrous conditions.

The new complexing compound tris-(3,6-dioxaheptyl)amine (TDA-1 [8]), $N(CH_2\text{-}CH_2\text{-}O\text{-}CH_2\text{-}CH_2\text{-}O\text{-}CH_3)_3$, was used to transport the organic salts. This compound efficiently transports salts of alkali cations, especially phenates and thiophenates, in apolar (or slightly polar) aprotic solvents such as aromatics, chloroaromatics and carbon tetrachloride [9]. Solubilization occurs by complexation of the cation. It has been also discovered that this complexing agent can strongly catalyze O-alkylation of phenols [10], aromatic nucleophilic substitution [11] and Ullmann synthesis [12] in solvents like chlorobenzenes or toluene. More importantly, truly catalytic amounts of TDA-1 can be used if the incoming nucleophile is softer than the leaving one, which is the common case for nucleophilic substitution [8]. Another advantage of TDA-1 is its low toxicity, in contrast with rigid structures such as crown-ethers and cryptands.

When we tested the catalytic capacity of TDA-1 in the synthesis of phenyl difluoromethyl ether [13,15]:



the reaction was found to be fast and exothermic during the early stages. The results are summarized in Table I. Kinetic measurements showed that the maximum yield (based on phenol) was obtained within almost three hours. The reaction was faster and the conversion of phenol higher in chloroaromatic solvents than in carbon tetrachloride but the yield of (difluoromethoxy)-benzene, based on converted phenol, was greater in carbon tetrachloride. In each case, the maximum yield of phenyl difluoromethyl ether was reached with at least 2.5 moles of solid NaOH per mole of phenol, as illustrated in Fig.1.

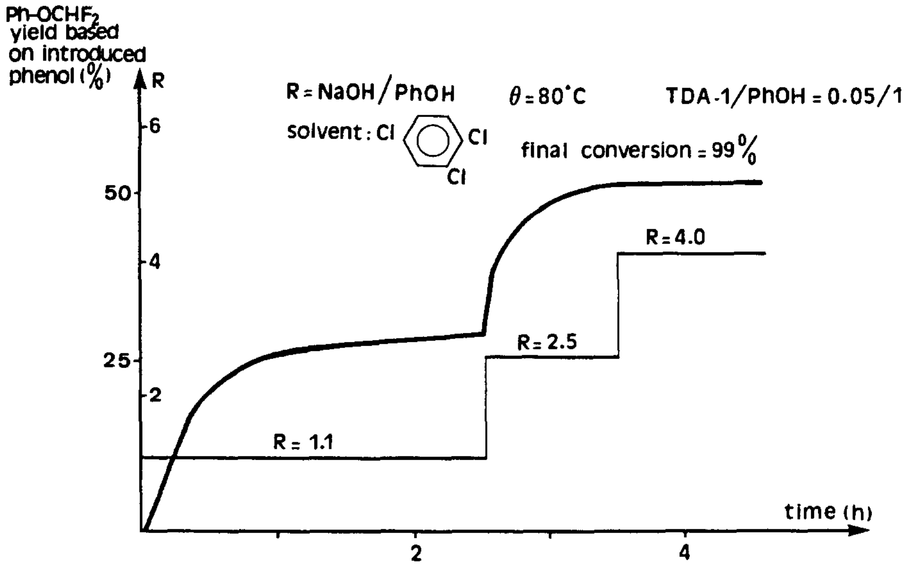
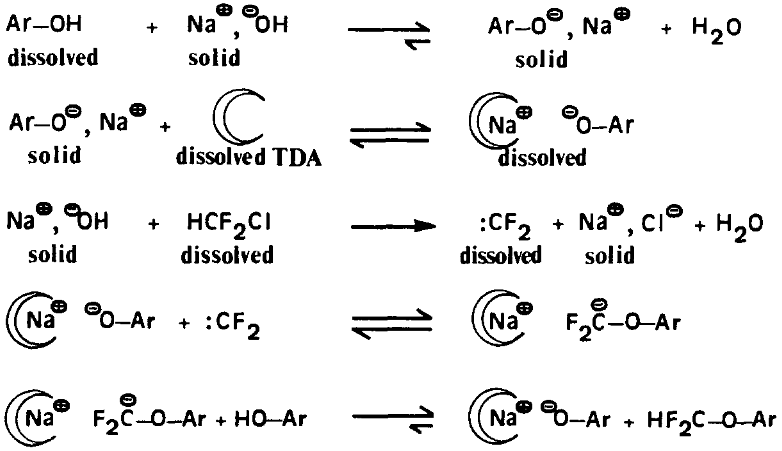


Fig.1. Yield of (difluoromethoxy)benzene v.s. time and ratio NaOH/phenol.

We suggest the following mechanism:



We postulate that the hard hydroxyl anion is not well solubilized by TDA-1 and that the deprotonations of phenol and chlorodifluoromethane are interfacial processes as in the classical Reimer-Tiemann reaction [14]. Furthermore, the

TABLE I

Difluoromethylation of phenol (solid-liquid system).

Solvent	T °C	Time (h)	Phenol conversion (%)	Yield on converted phenol(%)	Yield on introduced phenol(%)
$C_6H_5-CH_3$	85	2.7	96	44	42
CCl_4	70	3.0	84	57	48
CCl_4	70	7.5	87.5	58	51
$1,2,4-C_6H_3Cl_3$	20 ↓ 85	2.2	97	54	52

Conditions: NaOH/Ph-OH= 2.5/1 TDA-1/Ph-OH= 0.05/1

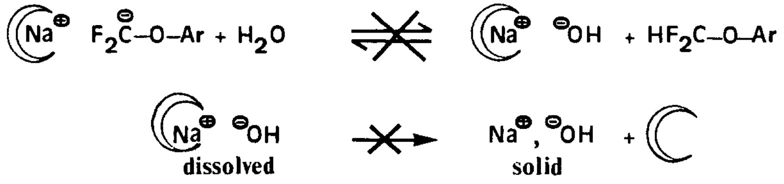
TABLE II

Difluoromethylation of substituted phenols (sol.-liq.)

R	Solvent	T °C	Time (h)	Conversion (%)	Yield on converted phenol (%)
4-CH_3	TCB	80	2.00	100	54
4-CH_3O	CCl_4	70	2.17	89	37
4-Cl	TCB	110	2.17	85	35
2-Cl	toluene	110	2.17	56.5	40
2-Cl	TCB	110	1.75	40.5	100
3-F	TCB	140	0.75	49	26
4-CF_3O	TCB	150	0.66	69	19
3-CF_3	TCB	140	1.42	75	31
4-CHO	toluene	105	1.17	24	100
4-CH_3CO	toluene	105	1.17	30	89
2or4-OH	TCB	110		0	

NaOH/Ar-OH= 2.5/1 TDA-1/Ar-OH= 0.05/1 TCB= $1,2,4-C_6H_3Cl_3$

catalyst recovery step can occur through the last equation of the preceeding scheme rather than through the "classical" step:



because water is not soluble in the medium and is "pumped out" by a hygroscopic compound such as solid sodium hydroxide.

Incidentally, it should be noted that the abstraction of water from the liquid reaction medium is probably the reason of one of our disappointments, namely the formation of rather high amounts of phenyl orthoformate (about 20% based on converted phenol). This observation can be interpreted as a consequence of the total aprotic character of the medium: the intermediary anion $Ar{-}O{-}CF_2^{\ominus}$ is not efficiently trapped by polarized hydrogens and can collapse into fluoride anion and carbene $Ar{-}O{-}\ddot{C}{-}F$, which is the precursor of aryl orthoformate:

$$\underset{(I)}{Ar{-}O{-}\overset{\ominus}{C}F_2} \overset{-F^{\ominus}}{\rightleftharpoons} \underset{(II)}{Ar{-}O{-}\ddot{C}{-}F} \overset{+Ar-O^{\ominus}}{\rightleftharpoons} \underset{(III)}{(Ar{-}O)_2\overset{\ominus}{C}{-}F} \overset{-F^{\ominus}}{\rightleftharpoons} (Ar{-}O)_2C:$$

$$\overset{+Ar-O^{\ominus}}{\rightleftharpoons} \underset{(IV)}{(Ar{-}O)_3C^{\ominus}} \xrightarrow{+ZO-H\ (Z=H,Ar)} (Ar{-}O)_3C{-}H$$

The reaction between chlorodifluoromethane and substituted phenols was studied also; the results are summarized in Table II. Note that the diphenates are not transported by the catalyst.

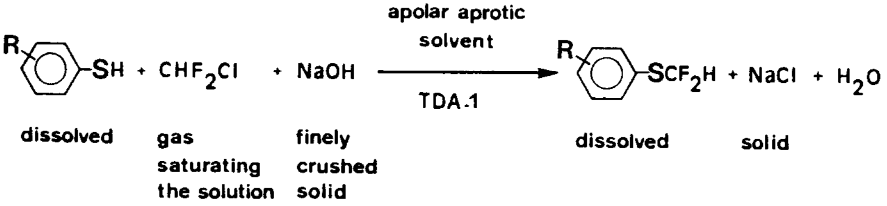
It is difficult to conclude on the intrinsic influence of the substituents because the observed yields result from:

- the proper reactivity of the substituted phenate,

- its ability to be complexed by the catalyst,
- the solubility of the so-formed complex in each solvent.

Concerning the amounts and nature of the polynuclear by-products detected by mass spectrometry, the situation looks rather complex. With very electron-donating substituents (R= CH_3, OCH_3) the presence of aryl orthoformates has not been accurately settled, probably because of the high instability of these compounds; with phenol itself as starting material, phenyl orthoformate has been quantified ; with 2-chlorophenol and 3-fluorophenol as starting materials, no aryl orthoformate has been identified but (diaryloxy)fluoromethane $(ArO)_2CHF$ was the major by-product, resulting from the protonation of anion (III); finally, with 3-(trifluoromethyl)phenol or 4-(trifluoromethoxy)phenol as starting materials, both (diaryloxy)fluoromethane and aryl orthoformate were detected. We suggest that this situation could be the result of two antagonist influences governing the generation of by-products: as the electron-withdrawing effect of R increases,the nucleophilicity of the phenate decreases but the electrophilicity of the corresponding aryloxycarbenes increases as suggested by Moss and Munjal's classification of carbenes [16].

Our technique has been also extended to some thiophenols, using the same conditions as for the phenols:



The results are summarized in Table III . Note that thiophenols are more reactive than the corresponding phenols, as indicated by higher reaction rates and yields under the same

TABLE III

Difluoromethylation of substituted thiophenols (solid-liquid system).

R	Solvent	T°C	Time (h)	Conversion (%)	Yield on converted thiophenol (%)
H	TCB	90	1.25	100	85
4-Cl	toluene	97	1.25	19	56
2-Cl	toluene	85	1.00	100	64

NaOH/Ar-SH= 2.5/1 TDA-1/Ar-SH= 0.05/1 TCB= $1,2,4-C_6H_3Cl_3$

TABLE IV

Comparative difluoromethylation of phenol and thiophenol under homogeneous conditions (polar protic solvent) or biphasic conditions (apolar aprotic solvent).

	Polar protic solvent (literature)	Apolar aprotic solvent (this work)
$Ph-OCHF_2$	yield= 65% [5] ($NaOH/H_2O$/dioxane)	yield= 54% (TCB/solid NaOH)
$Ph-SCHF_2$	yield= 63% [4a] (CH_3ONa/CH_3OH)	yield= 85% (TCB/solid NaOH)

TCB= 1,2,4-trichlorobenzene

N.B. Yields are based on introduced (thio)phenol.

conditions. This result is in contrast with published work carried out using a homogeneous protic medium (see Table IV). In protic solvents such as water or methanol, the nucleophilicities of phenates and thiophenates are levelled by solvation; whereas in aprotic solvents, the differentiated nucleophilicities of the unsolvated anions are observed.

The isolated yield obtained in protic solvents by Miller and Thanassi [5] is very difficult to reproduce because of the tediousness of the work-up. The major part of the dioxane is extracted with the desired product when treating the reaction medium with diethyl ether. Four washings of the ethereal solution with slightly basic water do not succeed in eliminating this dioxane and can destroy the crude (difluoromethoxy)benzene. The residual dioxane decreases the efficiency of the distillation which must be conducted upon solid sodium hydroxide or carbonate. Six final washings with distilled water are needed to extract completely the dioxane from the distilled product and obtain pure phenyl difluoromethyl ether. Thus, in our hands, only a 57% yield could be reached. This yield is relatively close to the one obtained using our heterogeneous procedure.

CONCLUSION

The advantages of our solid-liquid technique in preparing aryl difluoromethyl ethers and thioethers can be summarized as follows:

- the solvents required are cheap and readily available;
- the transporting agent is much less expensive and toxic than the usual ones (crown-ethers, cryptands) and is employed in truly catalytic amounts;

- as a result of an anhydrous procedure,the solvent can be recovered without any problem concerning azeotropes with water;
- this technique gives better yields of aryl difluoromethyl thioethers than the homogeneous one,
- the work-up of the reaction medium is very simple: after filtration, a classical distillation allows the separation between the solvent, the desired product and the unreacted phenol (thiophenol). No washing is needed, thus avoiding the possible degradation of the difluoromethyl ether (thioether).

EXPERIMENTAL

All the products were identified by ^{1}H or ^{19}F NMR spectroscopy and/or mass spectrometry (direct introduction or coupling with gas-phase chromatography). ^{1}H and ^{19}F NMR spectra were recorded, at 100 MHz and 93.65 MHz respectively, on a Jeol FX 100 spectrometer ($CDCl_3$ as solvent, $CFCl_3$ or tetramethylsilane as standards, positive ^{19}F chemical shifts downfield from $CFCl_3$) and mass spectra on a AEI MS 902 instrument (electron beam energy= 70 eV).

The progress of reactions was monitored by gas-phase chromatography (GPC) using a HP 5700 apparatus fitted with a thermal conductivity detector and a 3-metre long glass column (ø= 3.2 mm) packed with 10% OV 210 on chromosorb.

Reagents and solvents were all commercially available and were purified by standard procedures.

Typical procedure

In a 500 ml round-bottomed four-necked glass reactor, fitted with an efficient mechanical stirrer, a thermometer, a sintered gas inlet and a condenser (cooled down to −40°C), was charged: 200 ml of solvent, 0.2 mole of (thio)phenol, 20 g

(0.5 mole) of finely crushed sodium hydroxide and 3.2 g (0.01 mole) of tris-(3,6-dioxaheptyl)amine (TDA-1). This mixture was vigorously stirred while chlorodifluoromethane was bubbled into the solution. A noticeable exothermy was observed during the first minutes . Then, the medium was heated up to the desired temperature and maintained there during the time indicated in Tables I to III whilst passage of chlorodifluoromethane was continued. The progress of reactions were monitored by GPC.

When the maximum yield of (thio)ether was reached, the gas flow was interrupted and the reaction mixture cooled and filtered. The liquid organic phase was analyzed by GPC using an internal standard (generally monochlorobenzene) and the constituents were characterized by coupled GPC-MS. The solid part was dissolved in distilled water, the solution was acidified with dilute hydrochloric acid to pH=1 then extracted twice with diethyl ether. The unconverted (thio)phenol contained in the combined ethereal extracts was evaluated by GPC prior to and after adding a known amount of the same (thio)phenol.

The solvent and the required product were separated from the raw liquid organic phase by a rapid distillation through a Vigreux column. When necessary, the aryl difluoromethyl ether or thioether was rectified using a spinning-band distillation apparatus.

Physical properties of aryl difluoromethyl ethers and thioethers

- Mass spectra

The characteristic peaks for all the aryl difluoromethyl ethers are:M (molecular peak), M-19 (F loss), M-51 (CHF_2 loss) and 51 (CHF_2 peak). Those of bis-(aryloxy)fluoromethanes are: M (molecular peak), M-19 (F loss), M-ArO and M- 2 ArO.

TABLE V

Boiling points of compounds of structure R-C_6H_4-A-CHF_2

A	R	°C	mm Hg
O	H	76	85
O	4-CH_3	75	34
O	4-Cl	79	32
O	2-Cl	73	24
		90	45
O	3-CF_3	126	60
S	H	63	15
S	2-Cl	99	30

TABLE VI

^{1}H and ^{19}F NMR chemical shifts (ppm) of difluoromethyl ethers and thioethers (solvent: $CDCl_3$)

	^{1}H NMR (ref.: TMS)	^{19}F NMR ($CFCl_3$)
C_6H_5-$OCHF_2$	H arom. δ= 7.1 (m) CHF_2 δ= 6.3 (t) ^{2}J=78 Hz	δ= 76.0 (d)
4-CH_3-C_6H_4-$OCHF_2$	H arom. δ= 7.0 (m) CH_3 δ= 2.1 (s) CHF_2 δ= 6.3 (t) ^{2}J=80 Hz	δ= 75.7 (d)
4-Cl-C_6H_4-$OCHF_2$	H arom. δ= 7.0 (m) CHF_2 δ= 6.3 (t) ^{2}J=72 Hz	δ= 76.1 (d)
C_6H_5-$SCHF_2$	H arom. δ= 7.3 (m) CHF_2 δ= 6.8 (t) ^{2}J=60 Hz	δ= 90.0 (d)

The molecular peak for aryl orthoformates was not always detected, but significant fragments corresponding to the loss of one and two aryloxy groups were observed. Detailed spectra for two of the difluoromethyl ethers are as follows:

4-HOC-C_6H_4-$OCHF_2$ m/e= 172(M), 171(M-H), 153(M-F), 143(M-CHO), 121(M-CHF_2), 51(CHF_2)

4-CH_3CO-C_6H_4-$OCHF_2$ m/e= 186(M), 171(M-CH_3), 167(M-F), 143(M-Ac) 135(M-CHF_2), 51(CHF_2), 43(Ac)

- <u>Boiling points</u>

Our most accurate data for compounds of structure R-C_6H_4-A-CHF_2 (A= O,S) are listed in Table V.

- <u>NMR spectra</u>

Some characteristic examples are listed in Table VI.

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