Journal of Fluorine Chemistry, 17 (1981) 93–98
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Received: September 4, 1980

PRELIMINARY NOTE

Conversion of Alcohols into Monofluorides: Development of a Polymeric Analogue (PFAR) of the Yarovenko-Raksha Fluoroalkylamine Reagent (FAR), Et_2NCF_2CHFCl

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(2-Chloro-1,1,2-trifluoroethyl)diethylamine, Et_2NCF_2CHFCl, introduced by Yarovenko and Raksha in 1959 [1] and sometimes referred to as FAR (fluoroalkylamine reagent) [2], has been used extensively to convert alcohols into monofluorides ($ROH + Et_2NCF_2CHFCl \longrightarrow RF + Et_2NCOCHFCl + HF$), the procedure being hailed [2] as 'one of the simplest, most convenient, and safest fluorination techniques'. Despite its popularity and accessibility (from $CF_2{=}CFCl + Et_2NH$ [3]), however, FAR is not available commercially owing to its short shelf-life [2,5] which demands that it be put to use within 2-3 days of isolation, and preferably straightway. Ishikawa et al. [5] have circumnavigated this problem by developing an equivalent (in terms of efficacy) yet storable reagent ($Et_2NCF_2CHFCF_3$ + $Et_2NCF{=}CFCF_3$) based on perfluoropropene and diethylamine; our policy has been to aim for a polymer-anchored variation (PFAR) of Et_2NCF_2CHFCl, and recent results have clearly demonstrated the feasibility of this approach to the production of a transportable form of the Yarovenko-Raksha reagent.

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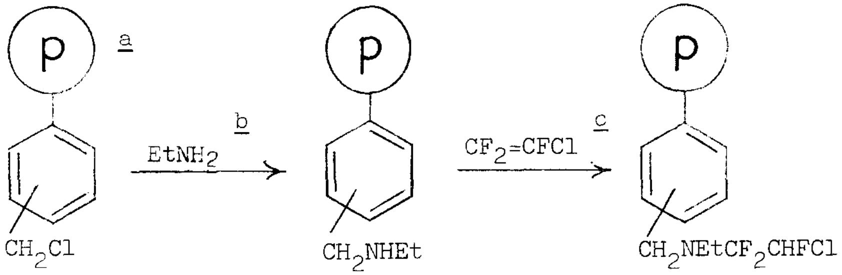


(I)

PFAR

SCHEME 1: Polymer-modification Route to PFARs

[a] The following halogenomethylated polymers were employed: (i) commercial copoly(styrene-divinylbenzene) (2% DVB) chloromethylated with $MeOCH_2Cl-SnCl_4$; (ii) poly(vinylbenzyl chloride); (iii) 50:50 and 80:20 copolymers of styrene and vinylbenzyl chloride; and (iv) crosslinked (2% DVB) polymers of type (iii). Standard techniques (free-radical initiation) were employed to procure polymers of type (ii)-(iv), using a *ca.* 2:3 mixture (Fluka) of *p*- and *m*-chloromethylstyrene.

[b] In DMF at room temperature with the linear (soluble) polymers [(ii) and (iii)]; in dioxan-water for the cross-linked (insoluble) variety (iv).

[c] Reactions were carried out by pressurising (*ca.* 2 atm) with $CF_2=CFCl$ (b.p. -27 °C) solutions or suspensions of the polymers in dichloromethane, toluene, dioxan, or dioxan-dichloromethane.

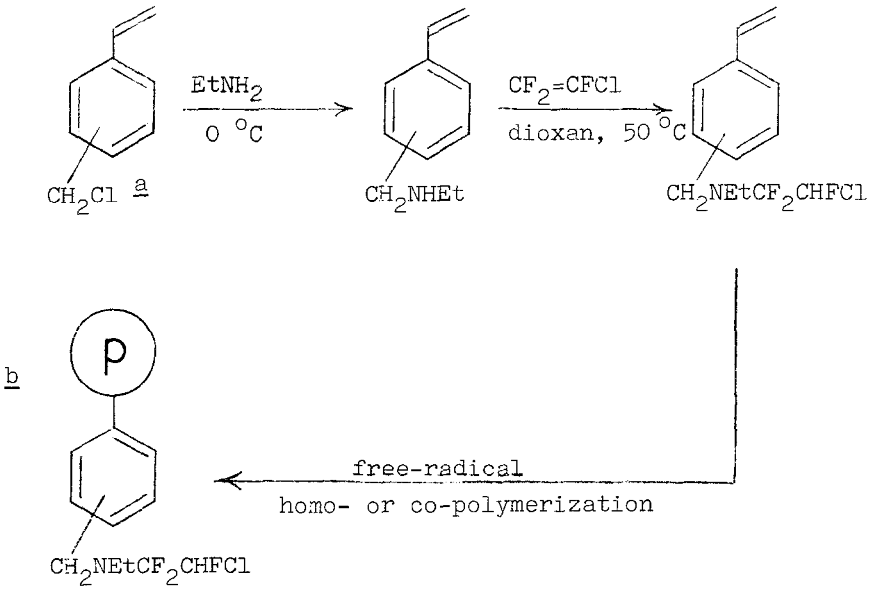
A polymer-modification route (Scheme 1) based on commercial beads of copoly(styrene-divinylbenzene) (2% DVB) chloromethylated with $MeOCH_2Cl-SnCl_4$ was chosen for the first attempt [6] to procure a macromolecular reagent that would mimic FAR. This failed at the final stage: the end-product contained less than one-third of the expected amount of combined fluorine and appeared not to react with cholesterol in boiling dichloromethane [7]. After demonstrating that the 'monomeric model' $C_6H_5CH_2NEtCF_2CHFCl$ [8] for PFAR will convert hexan-1-ol into 1-fluorohexane in 79% yield at 0 ^oC in dichloromethane, a range of aminated polymers of type I (Scheme 1) were prepared and treated with chlorotrifluoroethylene. As in the pioneering work [6], the products possessed elemental compositions inconsistent with FAR-loaded polymers and displayed no detectable fluorinating power towards hexan-1-ol; also, their solubilities were lower than expected, indicating that cross-linking had occurred in the final stage of production.

Suspecting that the polymer-modification route outlined in Scheme 1 suffers from the occurrence of intra- and inter-polymeric reactions (leading to chain-looping and crosslinking, respectively) between pendant FAR groups and unreacted amino functions [9] (hence the low halogen contents of the products, coupled with low F:Cl and Cl:N ratios), we turned to the direct route outlined in Scheme 2. This provided polymers carrying both $-CH_2NEtCF_2CHFCl$ and, owing to adventitious hydrolysis [10], $-CH_2NEtCOCHFCl$ groups [11], which smoothly and efficiently ($>$90% yield) converted hexan-1-ol, adamantan-1-ol, and cholesterol (S_N2 reaction [7]) into the corresponding monofluorides at 21 ^oC in dichloromethane [13]; as with FAR [14], dehydration ($\longrightarrow$ 4-t-butylcyclohexene) predominated over fluorination when 4-t-butylcyclohexanol (cis-trans mixture) was employed as substrate [15]. These PFARs retained their fluorinating capacities for months when stored under nitrogen in polyethylene bottles (Pyrex containers slowly became etched); as with polymer-anchored reagents in general, ease of product isolation attended their use [16].

1 N.N. Yarovenko and M.A. Raksha, J.Gen.Chem. U.S.S.R., 29 (1959) 2125.

2 C.M. Sharts and W.A. Sheppard, Org.Reactions, 21 (1974) 158.

3 With rigorous exclusion of moisture to prevent the easy hydrolysis $Et_2NCF_2CHFCl + H_2O \longrightarrow Et_2NCOCHFCl + 2HF$ [4], which causes the reagent to fume when exposed to Manchester air.



PFAR

SCHEME 2: Direct Route to PFAR s

[a] Ca. 2:3 mixture (Fluka) of p-and m-isomers.

[b] Soluble [homo- and co-(with styrene) polymers, using dicyclohexylperoxydicarbonate (DCHPD) at 45 °C as initiator] and insoluble (ter-polymers involving styrene and DVB, with DCHPD in benzene at 45 °C) polymers were produced.

4 R.L. Pruett, J.T. Barr, K.E. Rapp, C.T. Bahner, J.D. Gibson and R.H. Lafferty, J.Amer.Chem.Soc., 72 (1950) 3646.

5 A. Takaoka, H. Iwakiri and N. Ishikawa, Bull.Chem.Soc. Japan, 52 (1979) 3377.

6 A.-K. Barrage, M.Sc. Thesis, University of Manchester, 1976.

7 Efficient (> 85%) F-for-OH exchange (with inversion

of configuration) in this substrate can be effected with FAR at 0 °C in CH_2Cl_2 [J.C. Brial and M. Mousseron-Canet, Bull.Soc.chim. France, (1968) 3321].

8 Synthesised from benzyl chloride, as follows:
$C_6H_5CH_2Cl + EtNH_2$ (anhydrous) $\longrightarrow$ $C_6H_5CH_2NHEt$ (100%)
$\longrightarrow$ (with $CF_2{=}CFCl$ in dioxan at 50 °C)
$C_6H_5CH_2NEtCF_2CHFCl$ (57%).

9 FAR is known to react with secondary amines to give, eventually, tetrakis(dialkylamino)ethenes [4].

10 Use of metal polymerization equipment instead of Pyrex might alleviate this problem.

11 The most efficient FAR-loading achieved so far involved a 2% crosslinked polymer produced by copolymerizing *m*- and *p*-(4-chloro-2-ethyl-3,3,4-trifluoro-2-azabutyl)-styrene [12] with an equimolar proportion of styrene in the presence of DVB and dicyclohexylperoxydicarbonate (in benzene at 45 °C); the product contained 10.1% of fluorine (F: Cl ratio = 2.65:1), and showed only a weak C=O str. (1662 cm^{-1}) in the i.r. region attributable to pendant amide groups.

12 This mixture of monomers turns red and also undergoes hydrolysis ($CH_2{=}CHC_6H_4CH_2NEtCF_2CHFCl \longrightarrow CH_2{=}CHC_6H_4CH_2NEtCOCHFCl$) when exposed to glass or moist air at ambient temperature. It was stored under nitrogen in polyethylene at -30 °C prior to use.

13 The reactions were carried out batchwise, with stirring, for 24 hours (minimum reaction periods were not determined), using molar ratios (PFAR:alcohol) of not less than 2:1.

14 E.L. Eliel and R.J.L. Martin, J.Amer.Chem.Soc., 90 (1968) 682. These workers found that the ratio of fluorination to elimination is *ca*. 1:7.5 with FAR in ether.

15 The PFAR produced by 'homopolymerization' of $CH_2{=}CHC_6H_4CH_2NEtCF_2CHFCl$ (*m* and *p*) gave a fluorination to elimination ratio of 1:4.6. With a 2% (DVB) crosslinked *m*-/*p*-$CH_2{=}CHC_6H_4CH_2NEtCF_2CHFCl$-styrene copolymer suspended in benzene—dichloromethane, only the elimination product was detected.

16 Note that these direct-route PFAR s are only the third type of polymer-anchored fluorinating agent reported other than those of the ion-exchange variety [fluoride resins; see, for example, C.L. Borders, D.L. MacDonell and J.L. Chambers, J.Org.Chem., 37 (1972) 3549, and S. Colonna, A. Re, G. Gelbard and E. Cesarotti, J.C.S. Perkin Trans. I, (1979) 2248]; the other two are polystyrene-supported phenyliodine(III) difluoride [M. Zupan and A. Pollak, J.C.S. Chem.Comm., (1975) 715; M. Zupan, Coll.Czech.Chem.Comm., 42 (1977) 266] and N-trifluoroacetyl-nylon 6,6 [E.J. Günster and R.C. Schulz, Makromol.Chem., 180 (1979) 1891]. Intercalates of xenon fluorides in graphite have been developed as fluorinating agents [see, for example, H. Selig, L. Ebert, M. Rabinovitz, I. Agranat and C.-H. Lin, J.Amer.Chem. Soc., 98 (1976) 1601; M. Rabinovitz, I. Agranat, H. Selig, C.-H. Lin, and L. Ebert, J.Chem.Res. (S), (1977) 216; and I. Agranat, M. Rabinovitz, H. Selig and C.-H. Lin, Synthesis, (1977) 267; S.S. Yemil and H.B. Kagan, Tetrahedron Letters, 21 (1980) 277].