A Novel Reaction Medium: Perfluorocarbon Fluids

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The use of perfluorocarbon (PFC) fluids such as perfluorinated alkanes and alkylamines as inert medium for organic reactions is demonstrated with advantages summarized. PFC fluids have been found to be very useful in organic reactions where a medium is needed for refluxing and for separating a low boiling component, or where an extremely nonpolar/inert medium is required for reactions carried out under vigorous conditions. The PFC fluids are not miscible with most organic compounds and therefore offer good separatory properties that common organic solvents do not have.

The choice of a reaction medium may not be easy in some situations. For example, while facile transesterification is one of the few means to esterify an alcohol under neutral conditions, it is often difficult to find a medium to remove the resulting alcohol from the reaction mixture to shift the equilibrium. One either has to use excess reactants[1] (usually one with a lower bp or one which can form an azeotrope with the distilling alcohol) or incorporate a solvent such as benzene or toluene[2] to remove the alcohol displaced. Fresh solvent has to be added continuously to keep the reaction moving forward because the displaced alcohol is soluble in the solvent and the distillate can not be sent back to the reaction system. The good miscibility of alcohols with common organic reagents/solvents, therefore, has made these preparations economically and environmentally impractical. A solution to this problem is the use of perfluorocarbon(PFC) fluids as an immiscible medium in organic reactions.

The PFC fluids are a class of perfluorinated and saturated aliphatic compounds like perfluoroalkanes, perfluoroalkyl ethers and perfluoroalkylamines. They all have very unusual properties, such as high density and high stability, low solvent strength, and extremely low solubility in water and organic compounds (see Table 1). PFC fluids are, besides the fact that they can be used as immiscible reaction medium, suitable for reaction containing unstable reagents,[4] for heat transfer, and for temperature control. In polymer chemistry, PFC fluids can replace water in suspension polymerizations and should be particularly suitable for monomers which are not stable in water. It is reported that poly(lauryl methacrylate) prepared in fluorinated fluids is less sticky than in toluene.[5] We obtained polystyrene beads by suspension polymerization of styrene/divinylbenzene mixture in PFC fluids.

The versatility of using PFC liquids in organic reactions is demonstrated with 9 reaction samples ranging from transesterification to enamine formation (see Table 2). A commercially available PFC liquid[3] (bp 97 °C) was used in the reactions. The yields and the mp or bp of the products along with their literature references are summarized in Table 2. The actual yields for the reactions could be higher since the reaction conditions were not optimized.

It is reported[12] that molecular sieves can be used to selectively adsorb a low boiling alcohol in transesterifications. The sieves were contacted with the distillate and the effluent was returned to the reaction mixture. However, we found that the reaction is relatively difficult to complete due to inefficient alcohol adsorption by molecular sieves. Use of large amounts of molecular sieves will improve alcohol adsorption, but the yield was reduced since molecular sieves retain products too. In a comparison experiment, Reaction 4 in Table 2 was done in less than 4 hours (yield: 84%) whereas the method that employed molecular sieves took 20 hours (yield: 77%). Furthermore, the reactivity of molecular sieves prevents their application with many starting materials.

The characteristics of using PFC fluids as a reaction medium can be summarized as follows: 1) Easy separation; the PFC fluids can be separated at the end of reaction by simple filtration or phase separation instead of a vacuum distillation. This elimination of solvent distillation is especially desirable in the preparation of reactive products such as polymerizable monomer $CH_2=C(CH_3)CO_2C_{10}H_{21}$ (Reaction 6). The separated PFC fluid, which is usually free of reaction residues due to their poor organic solubility, can be reused in many cases without purification. 2) Fast reactions; we observed that reactions completed faster in PFC liquids than in toluene in our comparison test. For example, quantitative separation of water was obtained in 3.5 hours (yield: 82%) in PFC liquid vs 5 hours (yield: 81 %) in toluene in Reaction 5, and 3 hours (yield: 92%) in PFC liquids vs 5 hours (yields: 88 %) in Reaction 6, although reactions in toluene were carried out at higher temperatures due to boiling point difference (110 °C of toluene vs 97 °C of the PFC liquid). Please note that the above two examples are the only reactions in Table 2 where toluene can be used. 3) Whereas chemists have fewer and fewer organic solvents to choose from due to toxicity and environmental considerations, PFC fluids are available in a range of boiling points from 56 °C to 220 °C (see Table 1). Furthermore, PFC fluid vapor is about 17 times heavier than air. This allows for easy containment of the vapor, as well as providing an oxygen-free saturated vapor zone. We observed that reactions using PFC fluids are less colored than those using organic solvents. 4) The high purity (> 99.9), stability, and inert properties of PFC fluids make them especially suitable for reactions to be carried out at high temperature for a prolonged period, and for reactions which are sensitive to a polar environment, to moisture and/or to trace amounts of impurities.

Finally, it should be emphasized that the reactions presented in this article represent only a few examples of instances where PFC fluids can be used. We believe that many other reactions can benefit from the use of PFC fluids.

ω-Undecenyl Cyanoacetate (3); Typical Procedure:

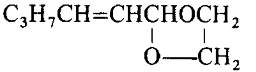
Methyl cyanoacetate (10.5 g, 0.105 mol), ω-undecenyl alcohol (17.4 g, 0.100 mol), titanium(IV) isopropoxide (0.25 g) and Fluorinert Fluid™ FC-77 (100 mL) (from 3 M Company, bp 97 °C) were

Table 1. Important Parameters of Some PFC Fluids[3]

PFC Fluids[a]	$C_5F_{11}NO$	C_6F_{14}	C_7F_{16}	C_8F_{18}	$(C_3F_7)_3N$	$(C_4F_9)_3N$	(C_5F_{11})
Boiling Point, °C	50.0	57.0	82.5	104.7	127.0	173.4	220.3
d_4^{25}, g/mL	1.70	1.68	1.73	1.78	1.82	1.88	1.94
Viscosity, 25 °C, cs	0.40	0.40	0.55	0.80	–	2.8	14.0
Solubility of Water, ppm	14	10	11	13	–	7.0	8.0

[a] $C_5F_{11}NO$: perfluorinated N-methylmorpholine; C_6F_{14}: perfluorinated hexane; C_7F_{16}: perfluorinated heptane; C_8F_{18}: perfluorinated octane; $(C_3F_7)_3N$: perfluorinated tripropylamine; $(C_4F_9)_3N$: Perfluorinated tributylamine; $(C_5F_{11})_3N$: perfluorinated tripentylamine

Table 2. Reactions Carried Out in PFC Liquids

Entry	Reactants	Product	bp/mmHg or mp, °C Observed	 Reported[Lit]	Yield (%)
1	$PhCO_2C_3H_7$ $HO(CH_2)_4OH$	$PhCO_2(CH_2)_4OCOPh$	84–5	82.5–83.5[6]	67
2	$PhCOOC_3H_7$ $PhCH_2OH$	$PhCO_2CH_2Ph$	117–8/0.10	133–5/0.50[7]	87
3	$CNCH_2CO_2CH_3$ $HO(CH_2)_9CH{=}CH_2$	$CNCH_2CO_2(CH_2)_9CH{=}CH_2$	128–30/0.03	–	87
4	$C_6H_{11}CH_2CO_2C_2H_5$ $C_{10}H_{21}OH$	Decyl Cyclohexylacetate	113–5/0.02	–	84
5	$CH_2{=}C(CH_3)CO_2H$ $PhCH_2OH$	$CH_2{=}C(CH_3)CO_2CH_2Ph$	93–4/0.70	56/0.15[8]	82
6	$CH_2{=}C(CH_3)CO_2H$ $C_{10}H_{21}OH$	$CH_2{=}C(CH_3)CO_2C_{10}H_{21}$	83–5/0.1	99–100/1.3[9]	92
7	$C_3H_7CH{=}CHCH(OEt)_2$ $HOCH_2CH_2OH$	 $\begin{array}{l} C_3H_7CH{=}CHCHOCH_2 \\ \qquad\qquad\qquad \vert \qquad \vert \\ \qquad\qquad\qquad O{-}CH_2 \end{array}$	50–1/2.6	–	64
8	$CH(OEt)_3$ Cyclohexanone	1,1-Diethoxycyclohexane	45–46/2.5	74–6/15[10]	41
9	morpholine cyclohexanone	1-Morpholino-1-cyclohexene	92–93/2.0	123–7/12[11]	53

mixed in a 2-necked 500 mL round-bottom flask equipped with a modified Dean-Stark trap. The trap, which is available from Ace Glass, allows the denser phase to be returned to the reaction mixture (the PFC fluids with a density around 1.6–1.9 g/mL are heavier than most organic fluids). This mixture was heated to reflux until approximately 3 grams of MeOH were separated (in 2 hours). It was then cooled to r.t. The top organic layer, after being separated from the bottom FC fluids and vacuum distilled, afforded 23.5 g of product (bp 128–130 °C/0.03 mmHg, yield 87 %).

^1H NMR ($CDCl_3$): δ = 5.80 (m, 1 H), 5.02–4.91 (m, 2 H), 4.20 (t, 2 H), 3.47 (s, 2 H), 2.03 (m, 2 H), 1.67 (m, 2 H), 1.35–1.28 (m, 12 H).

^{13}C NMR ($CDCl_3$): δ = 163.1, 139.2, 114.1, 118.1, 67.1, 29.4, 29.4, 29.2, 29.1, 28.9, 28.4, 25.7, 25.7, 24.8.

Decyl methacrylate (16); Typical Procedure:

Decyl alcohol (38.0 g, 0.24 mol), methacryclic acid (21.5 g, 0.25 mol, containing 250 ppm 4-methoxyphenol), *p*-TsOH (0.5 g) and FC-77 (150 mL) were mixed into a 2-necked 500 mL round-bottom flask equipped with a modified Dean-Stark trap as described above. The mixture was brought to reflux and around 4 mL of water was collected in 3 hours. The top organic layer, after being separated from the bottom FC-77 layer, was washed with 5 % NaOH (30 mL), followed by water (3 × 50 mL) and then dried ($MgSO_4$). 55.0 g of crude product (96 % purity by GC) was obtained. 49.6 g of pure decyl methacrylate was obtained upon further distillation (bp 83–85 °C/0.01 mmHg, lit. 99–100 °C/1.3,[9] yield: 91.5 %).

^1H NMR ($CDCl_3$): δ = 6.1 (s, 1 H), 5.6 (s, 1 H), 4.2 (t, 2 H), 2.1 (s, 3 H), 1.8 (m, 2 H), 1.4 (bs, 14 H), 1.0 (s, 3 H).

All of the remaining reactions in Table 2 were carried out using the general procedures described in the above two examples. The purity of the products was established by bp/mp (see Table 2 for references) and GC, and the structures were confirmed by NMR spectra.

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