ORGANIC LETTERS

2009
Vol. 11, No. 15
3190−3193

Phase-Vanishing Reactions with PTFE (Teflon) as a Phase Screen

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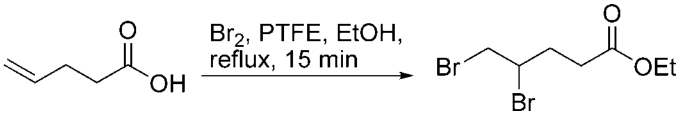
Received May 7, 2009

ABSTRACT



Phase-vanishing reactions are triphasic reactions, which involve a reagent, a liquid perfluoroalkane, and a substrate. In a phase-vanishing reaction with PTFE tape as the phase screen instead of a liquid perfluoroalkane, there is no limitation related to the density of a phase and the denser phase can be in the top layer. The reactions were faster compared to traditional PV reactions, and it was possible to carry out sequential and tandem reactions and reactions under a reflux.

Phase-vanishing (PV) reactions are triphasic reactions, which involve a reagent, a liquid perfluoroalkane, and a substrate.[1−11] The perfluoroalkane, which is in the layer between the two, acts as a phase screen. It is inert and is used to separate the reactants. As the reagent diffuses through the perfluoroalkane layer, it reaches the substrate layer and reacts with it. Thus, the reaction proceeds at a moderate rate, instead of a vigorous and often violent reaction if the two reactants were mixed without a solvent. In the course of the reaction, the reagent disappears ("vanishes").

PV conditions allow for reactions that otherwise would be too vigorous without a solvent to be performed on neat reagents.[12,13] This considerably simplifies the work-up. However, fluorinert liquid FC-72 (C_6F_{14}) has a high global warming potential (GWP ∼10,000) and atmospheric lifetime of 3200 years.[14] Although in a PV reaction FC-72 is used in a closed system and can be either reused or recovered for future use, it also has a low boiling point, and one has to be careful to minimize losses. In addition, some solvents, reagents, and reaction products are partially soluble in FC-72,[5,12,13,15] which limits our ability to either reuse or completely recycle it.

Ryu and Curran have reported advantages in using heavier liquid perfluoro compounds as phase screens.[16] Herein we report use of a solid perfluoro compound, PTFE (Teflon tape), as a phase screen.

In a phase-vanishing PTFE (PV-PTFE) reaction setup, the substrate in a solvent was placed in a reaction vessel, such as a vial, test tube, or flask. The reagent was placed in a delivery vessel, such as a glass tube, and sealed on both ends with PTFE tape. This tube is then inserted into the reaction vessel so that both reactants are in contact with the PTFE

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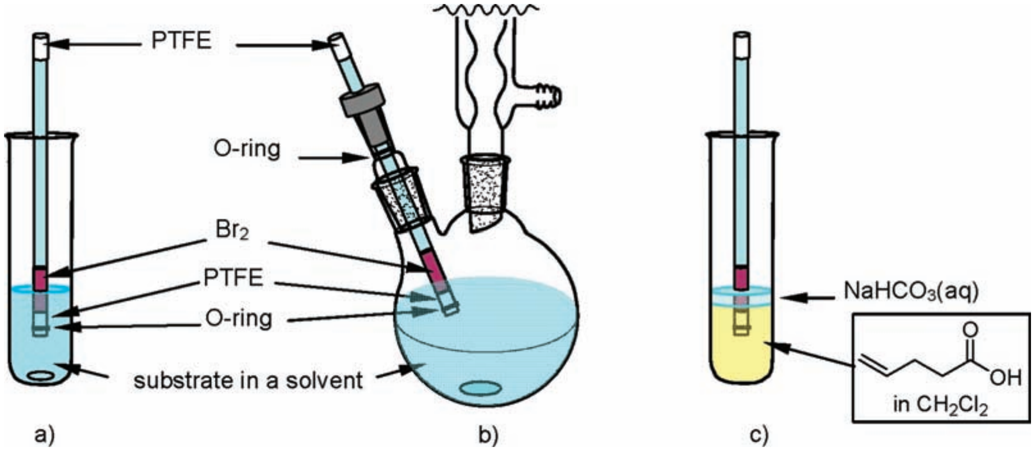


Figure 1. Phase-vanishing reaction with PTFE as a phase screen: (a) a simple ambient temperature reaction, (b) reaction under a reflux, and (c) a tetraphasic reaction.

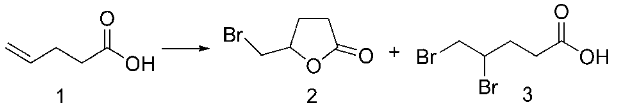
phase screen (Figure 1a). Additional experimental details including modification of the reaction setup to carry out reactions under reflux (Figure 1b) and tetraphasic reactions (Figures 1c and 4) are provided as Supporting Information. It was possible to control the reaction rate by adjusting the thickness of the PTFE layer and the rate of stirring, with a higher rate of stirring resulting in a faster reaction.

A number of solvents including dichloromethane, ethyl acetate, benzene, and toluene worked very well. Hexanes were suitable in only a few cases. Among the solvents, dichloromethane passed through PTFE the easiest. Due to its high permeability, dichloromethane solution was often drawn into the delivery tube. The result was a very fast and sometimes vigorous reaction. As the amount of the solution drawn into the tube could be rather large, the PTFE screen should be secured with an O-ring or additional PTFE tape. Otherwise the pressure of the column of liquid on the PTFE screen could cause it to fail and for the solution to be delivered into the flask. In general, it was not a problem unless it happened very early in the reaction when the result was a very vigorous reaction. A way to prevent dichloromethane from being drawn into the delivery tube is to either provide a pressure outlet or to carry out a tetraphasic reaction (Supporting Information, page S9).

PTFE exhibited different permeability toward different reagents. Some of the reagents ($TiCl_4$, $(COCl)_2$) passed so easily through PTFE that it did not present a barrier at all. Those reagents had to be used in a solvent such as dichloromethane. Most reagents (Br_2, $SOCl_2$, CH_3CH_2COCl, aqueous H_2O_2) passed through PTFE at a modest rate, and the reaction rate could be controlled by the thickness of PTFE or the number of layers of PTFE used to form a screen. Finally, PTFE exhibited very low permeability toward some substrates, most notably phthalates (phthaloyl chloride, phthalate esters).

Bromination with PTFE as a phase screen worked well. However, the outcome was dependent on the solvent, with dichloromethane usually giving the best results. Interestingly, while bromine worked very well, iodine monochloride, which gave good results in PV reactions with FC-72 phase screen,[12,13] worked very poorly and reactions with it were not of a preparative value.

Table 1. PV-PTFE Bromination of 4-Pentenoic Acid (**1**)



entry	conditions	**2** (%)[a]	**3** (%)[a]
1	Br_2/PTFE/CH_2Cl_2/$NaHCO_3$(aq), rt, 5 min[a]	82	4
2	Br_2/PTFE/EtOAc, reflux, 15 min	72	9
3	Br_2/PTFE/CH_3CN/Na_2CO_3(s), rt, 15 min	74	*b*
4	Br_2/PTFE/CH_2Cl_2, rt, 5 min	0[c]	94

[a] Isolated yields. [b] Some **3** was observed but not isolated (Supporting Information). [c] GC−MS analysis.

PV-PTFE reaction of 4-pentenoic acid (**1**) with bromine allowed the selective preparation of either the lactone **2** (Table 1, entries 1−3) or the diacid **3** (Table 1, entry 4). This is a considerable improvement over the same reaction carried out in dichloromethane, under solvent-free conditions, or under a traditional phase-vahishing conditions with FC-72 as a phase screen, all of which gave mixtures of the products.[12] The best yield of the bromolactone **2**, as well as the highest purity (Table 1, entry 1), was obtained when a bromine-containing tube was inserted into a solution of 4-pentenoic acid in dichloromethane and an aqueous solution of sodium bicarbonate was added to the top of the dichloromethane phase in a modification of Ryu's tetraphasic procedure (Figure 1c).[17] Alternatively, a reaction in EtOAc under reflux provided the lactone **2** in 72% yield along with a small amount of the 4,5-dibromopentanoic acid (**3**) (9%) (Table 1, entry 2). Finally, good yields were obtained by performing PV-PTFE bromolactonization on sodium 4-pentenoate in acetonitrile (Table 1, entry 3).

PV-PTFE bromination of 3-butenoic acid (**4**) gave 3,4-dibromobutanoic acid (**5**) as the major product. In dichloromethane, the reaction was completed in ~5 min at room temperature (Figure 2). The crude product gave a satisfactory ^{1}H NMR. 3,4-Dibromobutanoic acid had been prepared in a conventional bromination reaction in carbon tetrachloride at 0 °C and addition of bromine over 1 h.[18] PV-PTFE bromination of 3-butenoic acid shows a preference for dibromination as opposed to cyclization. A possible reason is that the 5-*endo* cyclization is a disfavored process.[19] Interestingly, we did not observe formation of any 4-*exo* cyclization product **7**, even though it is expected to be favored according to Baldwin rules.[19] The best yield of 5-bromodihydrofuran-2(3*H*)-one (**6**) was obtained by conducting a tetraphasic PV-PTFE reaction in dichloromethane and adding an aqueous bicarbonate as the top phase (Figures 1c and 2).

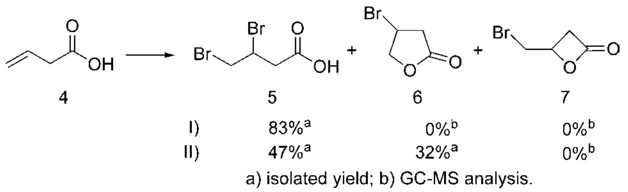


Figure 2. PV-PTFE bromination of 3-butenoic acid (**4**) under (I) triphasic (Br_2/PTFE/CH_2Cl_2, rt, 5 min) and (II) tetraphasic (Br_2/PTFE/CH_2Cl_2/$NaHCO_3$(aq), rt, 5 min) conditions.

Bromination of cyclohexene (**8**) under PV-PTFE conditions worked very well in dichloromethane to give rather pure *trans*-1,2-dibromocyclohexane (**9**) in good yield (Table 2, entry 1). The reaction was completed in about 5 min. In ethyl acetate, the reaction was somewhat slower, and formation of *trans*-1,2-dibromocyclohexane was accompanied by a small amount of 3-bromocyclohexene (**10**) (<10% according to GC analysis) (Table 2, entry 2). The reaction failed in hexanes (Table 2, entry 3). Cyclohexene was successfully brominated in good yields under traditional PV conditions.[1,11,13]

Successful PV bromination of phenol has been reported.[4] PV-PTFE bromination of phenol (**11**) in water resulted in formation of 2,4,6-tribromophenol (**12**). A direct addition of bromine to a solution of phenol in water was highly exothermic. A PV-PTFE reaction with a single layer of PTFE as a phase screen was more moderate, and when two layers of PTFE were used, there was only a slight increase in the reaction temperature (Figure 3). Although the reaction product was isolated in a high yield, it was impure.

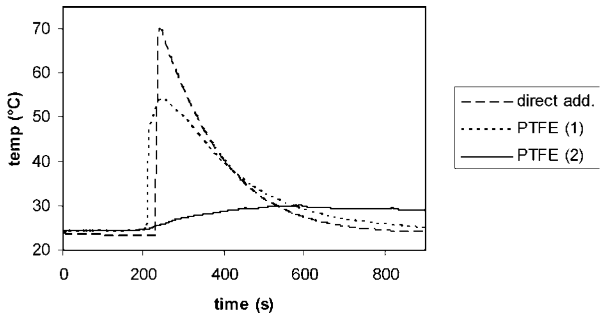


Figure 3. Temperature change in the course of a bromination of phenol in water by a direct addition, PV reaction with one (1) and two (2) layers of PTFE.

There was an interesting effect of FC-72 on the PV-PTFE reaction in water. Curran's original application of triphasic PV conditions was to both remove a fluorous tag and purify the organic product in the course of the reaction.[20] Thus, in an alternative tetraphasic reaction, we added FC-72 as a fourth phase to a PV-PTFE bromination of phenol (Figure 4). Solid 2,4,6-tribromophenol, although more dense than FC-72, formed a crust on the water/FC-72 interface and additional product deposited on the top of it. At the same time, liquid impurities diffused through FC-72 and collected on the bottom. Both NMR and GC of the product obtained by filtration showed that it was pure (Table 2, entry 4). Tetraphasic PV-PTFE reaction is a useful alternative to some recently published methods for bromination of phenols.[21,22] The outcome of PV-PTFE bromination of phenol (**11**) was solvent-dependent. A reaction in dichloromethane gave 2,4-

Table 2. Phase-Vanishing Reactions with PTFE as a Phase Screen

entry	reaction vessel	addition tube	products (%)[a]
1	cyclohexene (**8**), CH_2Cl_2, 5 min	Br_2	*trans*-1,2-dibromocyclohexane (**9**) (70)
2	**8**, EtOAc, 15 min	Br_2	**9** + 3-bromocyclohexene (**10**) (~85%; **9/10** = 9/1[b])
3	**8**, hexanes, 12 h	Br_2	0[b]
4	phenol (**11**), H_2O, FC-72, 3 h	Br_2	2,4,6-tribromophenol (**12**) (87)
5	**11**, CH_2Cl_2, 1 h	Br_2	2,4-dibromophenol (**13**) (74)
6	menthol (**14**), CH_2Cl_2, 1 h	$(COCl)_2$, CH_2Cl_2	dimenthyl oxalate (**15**) (90)
7	**14**, CH_2Cl_2, 1 h	propionyl chloride	menthyl propionate (**16**) (92)
8	**1**, EtOH, reflux, 15 min	Br_2	ethyl 4,5-dibromopentanoate (**17**) (75)

[a] Isolated yield. [b] GC−MS analysis.

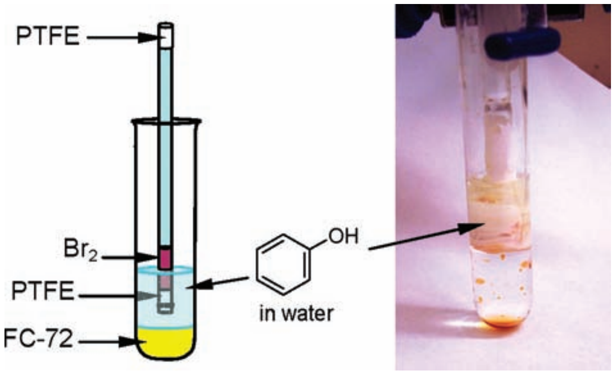


Figure 4. Tetraphasic bromination of phenol (bromine-PTFE-aqueous solution of phenol-FC-72). Photograph shows a completed reaction with the solid product in the aqueous phase and impurities at the bottom.

dibromophenol (**13**) as the major product (74%) even with an excess (3 equiv) of bromine (Table 2, entry 5).

Another bromination that gives insoluble solid products, bromination of both *cis*- or *trans*-stilbenes, failed. The reaction occurred at the interface between bromine and a solution of stilbene. The solid products coated PTFE and prevented any further reaction. Stilbenes were successfully halogenated under PV conditions with a liquid (FC-72) phase screen.[13]

Dimenthyl oxalate (**15**) and menthyl propionate (**16**) were prepared in good yields by addition of the corresponding acyl chloride to a solution of menthol (**14**) in dichloromethane (Table 2, entries 6 and 7). As the permeability of PTFE toward oxalyl chloride is high, a solution of oxalyl chloride in dichloromethane was used. Upon completion of the addition, the reaction mixture was stirred for 0.5−2 h at room temperature to complete the reaction.

One of the advantages of using PTFE instead of a liquid phase screen is that it allows for a reaction to be carried out under a reflux. This was exploited in a PV-PTFE tandem esterification−bromination of 4-pentenoic acid in refluxing ethanol to obtain ethyl 4,5-dibromopentanoate (**17**) (Table 2, entry 8). A PV-PTFE reaction at room temperature afforded a ∼1:1 mixture of 4,5-dibromopentanoic acid (**3**) and ethyl 4,5-dibromopentanoate (**17**). A tandem PV bromination−transesterification reaction of 4-pentenoic acid in ethyl acetate with FC-72 as a phase screen gave the dibromoester **17** in 41% yield.[12]

PTFE offers some advantages compared to a liquid perfluoro phase screen. PTFE tape is inexpensive and easy to use and may be reused. This is an alternative not only to PV reactions but also to any reaction that involves a slow addition (e.g., by means of syringe drive). In addition, there is no limitation related to densities of reactants, and a PTFE phase screen may be used to separate reactants that are either both more or less dense than the phase screen. As a result, one can use conventional glassware (for example, there was no need to use a U-tube to separate two reactants lighter than the phase screen), which makes conducting tandem or sequential reactions easier and more convenient. Thus, a reagent such as bromine, with a density higher than that of the phase screen, can be the top phase, which makes a reaction under a reflux possible. Reactions can be performed in the presence of an additional phase as tetraphasic reactions. As with the PV reactions involving a liquid phase screen, PTFE phase screen provided a means for slow delivery of reagent. In general, reactions with a PTFE phase screen were faster than PV reactions, and the reaction rate could be controlled by adjusting the thickness of the PTFE screen. However, in some cases, such as in the use of iodine monochloride as a reagent or when the precipitated products form a barrier on the PTFE tape, a traditional PV reaction with a liquid phase screen remains the best choice.

Acknowledgment. We thank Salvatore Lepore, Department of Chemistry, Florida Atlantic University, for helpful discussions and Nicole Windmon from Department of Chemistry, Florida Atlantic University, for recording NMR spectra. Partial financial support from the Wilkes Honors College of Florida Atlantic University is gratefully acknowledged.

Supporting Information Available: Additional experimental details and MS and ^{1}H NMR spectra of isolated compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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