An optimised procedure for PTFE phase vanishing reactions: an improved reaction design and the use of reagents adsorbed on silica Brendon A. Parsons^{a,b}, Olivia Lin Smith^a and Veljko Dragojlovic^{a*}

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While the phase-vanishing (PV)-PTFE reaction design works well with a broad range of substrates and reaction conditions, there are occasional problems. A description of the problems and their importance, including their effects on the reaction outcome and ways to address them, are discussed. Details of an improved design, a hybrid of previously reported PV-PTFE and solvent-free PV-PTFE designs, is presented, as well as the use of silica-supported reagents.

Keywords: phase screen, PTFE, semipermeable membrane, synthesis design, bromination

The phase-vanishing (PV) reaction design is relatively new. It replaces the reaction solvent with an inert perfluoroalkane as a phase screen.¹⁻¹⁶ The solvent provides a reaction medium for the reactants and it also helps dissipate the heat of the reaction. The role of the fluorous phase screen is to separate the reagent from the substrate, which provides a way to carry out reactions under ambient conditions on neat reactants. In the course of the reaction, the reagent diffuses through the phase screen and the reagent phase vanishes (Fig. 1a). The phase-vanishing method offers some advantages compared to traditional methods. The experimental design is simple and there is no need for a delivery system such as a syringe drive. Diffusion through the phase screen enables the slow and controlled delivery of reactants. Thus, exothermic reactions normally carried out at low temperatures (typically -78 to 0 °C) can both be conducted at an ambient temperature and the reactions that otherwise would be too vigorous without a solvent can be carried out on neat reagents.4,8,15,16

Bromination was one of the first reactions that was developed as a phase-vanishing fluorous reaction.^{1,2} Other groups³⁻¹⁴ and ourselves^{15,16} have made improvements to the original PV procedure and applied it to various systems.

We introduced PTFE (polytetrafluoroethylene, Teflon) tape as phase screen (Fig. 1b) in phase-vanishing PTFE (PV-PTFE) reaction design.¹⁷⁻²¹ This experimental design also offers more control of the reaction conditions and delivery of the reagent. The original PV-PTFE design consisted of a PTFE-sealed reagent tube immersed in a solution of the substrate in a suitable solvent.¹⁷ It has been since modified to be carried out under solvent-free conditions¹⁸ and further developed to utilise PTFE-sealed vials for the delivery of the reagent.²⁰





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The two methods, PV and PV-PTFE, are complementary. PV-PTFE is inexpensive, more environmentally friendly and relies on readily available laboratory materials. It works best with highly reactive reagents whether they be liquids, or high vapour pressure solids. However, it has some limitations. The reaction setup may be more time consuming and there are some limitations as to suitable reagents and substrates. The more conventional fluorous PV method requires the use of a costly fluorous solvent and work up may be somewhat more involved owing to the need to carefully separate the aqueous phase from the product phase, and to appropriately handle the fluorous solvent to avoid loss. On the other hand, this method can accommodate a greater variety of reactants. Reviews of PV^{12,13} and both PV and PV-PTFE reactions¹⁹ have been published.

We now address the complications that we encountered in the development and implementation of PV-PTFE reactions. As a result, a new hybrid PV-PTFE reaction design and the use of silica-supported reagents were introduced.

Results and discussion

While PV-PTFE reaction design generally performed very well, we encountered some problems. These include the reaction solvent being drawn or forced into the delivery tube, the surface of the PTFE tape being clogged with the product, the reaction of a volatile substrate with the reagent on the surface of the PTFE tape, accumulation of solvent in the delivery tube when a hybrid PV-PTFE reaction design was employed, excessive rate of reagent delivery and local accumulation of the reagent.

The above problems do not appear in each trial and not all of them appear regularly. Furthermore, most of them do not affect the reaction outcome. However, they may make performing the reaction and isolation of pure product more laborious and less elegant. Therefore, we decided to address them and to further optimise the reaction design.

Solvent being drawn or forced into the delivery tube

A draw of the solvent into the delivery tube is one of the most consistent and reproducible problems we encountered (Fig. 2). We explored the causes of it in our recent publication.²¹ While a draw of the solvent into the delivery tube usually did not affect the reaction outcome, it made the reaction conditions more difficult to control, sometimes complicated the reaction work-up and, in general, made the method less efficient and elegant.

The main problem with the solvent being drawn into the delivery tube was that it dilutes the reagent and the reaction may occur in the tube where the concentration of the reagent is high (Figs 3a and 3b). There are several ways to avoid the solvent being drawn into the delivery tube. First, one can select the solvents that



Fig. 2 Draw of the solvent into the delivery tube. The initial solvent level is marked by a line. The solvents were acetone (with a blue ink added) in the flask and water (with a red ink added) in the delivery tube. The total elapsed time was 25 min.



Fig. 3 (a) In a typical PV-PTFE reaction design delivery tube is immersed into the solvent. (b) Such a set-up allows solvent to be drawn into the delivery tube. (c) A modified design in which the delivery tube just touches the surface of the solvent reduces solvent uptake. (d) Solvent-free PV-PTFE design. (e) A hybrid reaction design.



Fig. 4 Bromination of trans-stilbene by means of a hybrid reaction design.

have low tendency to be drawn into the delivery tube.²¹ Another involves a small change in the design, where the delivery tube is not immersed into the reaction solution, but instead just touches it (Fig. 3c). That way, as soon as some solvent is drawn into the tube its level drops below the bottom of the delivery tube and the uptake stops.²¹

Finally, the most effective way to prevent solvent uptake is to keep the delivery tube above the solvent level. That is a so-called hybrid PV-PTFE reaction design (Fig. 3e) as it combines features of the solvent-free¹⁷ (Fig. 3d) and PV-PTFE¹⁸ designs (Fig. 3a). The hybrid reaction design enables clean and efficient delivery of a volatile reagent to the reaction mixture. The reagent is delivered into the gas phase above the reaction mixture and is then absorbed



by it. Such a design makes a draw of the solvent into the tube impossible. However, it is restricted to the delivery of volatile reagents such as bromine and iodine monochloride. Suitable solvents included dichloromethane and, a more environmentally friendly, ethyl acetate.

A suitable illustration of hybrid PV-PTFE reaction design is bromination of *trans*-stilbene **3** in ethyl acetate (Fig. 4, Scheme 1).



Scheme 2



Fig. 5 Reaction set-ups that prevent the solvent being forced into the delivery tube (a) A general set-up with a side arm on the left for pressure equalization, the delivery tube in the middle and a flask for addition of solids attached to the right neck of the flask. (b) An example of a reaction setup to carry out the preparation of DNPO. (c) Chemiluminescence of DNPO prepared in the course of the PV-PTFE reaction.

meso-Dibromostilbene **2** precipitates out of the solution, while the isomeric d,l-dibromostilbene **6** remains dissolved.

In some cases the solvent was forced into the delivery tube. Although the end result was the same as the solvent being drawn into the delivery tube, the cause was different and was easy to address. We encountered this problem when carrying out the preparation of bis(2,4-dinitrophenyl) oxalate (DNPO) 4 from 2,4-dinitrophenol (2,4-DNP) 3 and oxalyl chloride in dichloromethane [Scheme 2 (1)]. We avoided the use of a base, such as triethylamine, as we wanted a pure product that did not need any further purification. DNPO is highly moisture sensitive and an attempt at further purification risks hydrolysis of the product or, at best, considerably reduces the yield. In the absence of a base, the reaction proceeds with the evolution of gaseous hydrogen chloride. Thus, in a closed system there was a pressure build-up and some solvent was forced into the delivery tube. By simply placing a partially inflated nitrogen filled balloon on one of the necks of the reaction flask, pressure buildup was prevented and no solvent was drawn into the delivery tube (Fig. 5a and b). The reaction proceeded smoothly to give DNPO, which upon treatment with H₂O₂ mixture exhibited intense and long lasting chemiluminescence (Fig. 5c) [Scheme 2(2)].²²⁻²⁴

Surface of the PTFE tape being clogged with the product

In a conventional PV-PTFE reaction, the delivery tube was immersed into the solution. Occasionally an insoluble product formed on the surface of the PTFE tape and clogged it. That prevented further delivery of the reagent and terminated the reaction. An example is the previously described bromination of *trans*-stilbene **1**. The product, *meso*-dibromostilbene **2**, forms an insoluble coat on the surface of the PTFE tape and further reaction stops. Although carrying out the reaction with vigorous stirring may help prevent clogging of the PTFE tape, the best solution was the use of a hybrid PV-PTFE reaction design as shown in Fig. 3e. Alternatively, bromination of *trans*-stilbene can be carried out under solvent-free PV-PTFE conditions.^{18,20}

Reaction of a volatile substrate on the surface of the PTFE tape In a solvent-free reaction, sometimes a substrate reacted with the reagent on the surface of the PTFE tape coating it with the product. That was the case when a volatile substrate was used and the delivery tube was close to the surface of the substrate. Sometimes, all that was necessary to avoid a reaction on the PTFE surface was to find an optimum distance of the delivery tube to the surface of the substrate. If the delivery tube was too close, the reaction was rapid and occurred on the PTFE tape. If the delivery tube was placed at a sufficient distance from the substrate, the formation of the product on the surface of the PTFE tape was reduced.

Thus, with a non-volatile *cis*-stilbene **5** as the substrate, there was no observed reaction on the PTFE tape in repeated trials (Fig. 6, Scheme 3). The solid product **6** was obtained in high yield and purity, even when the delivery tube was placed close to the surface of the substrate.

A solvent-free reaction of volatile liquid 2,3-dimethyl-2butene **7** with bromine illustrates this problem (Fig. 7, Scheme 4). There was a rapid reaction on the surface of PTFE tape.



Fig. 7 A volatile substrate reacted with the reagent on the surface of PTFE tape coating it with the product.



Scheme 3

In this case, the product was scraped off the tape and left in a fumehood until the excess of bromine evaporated. By-products, apparently a result of allylic free radical substitution, were observed by GC-MS analysis.

The problems involving volatility of some substrates can be addressed by various measures. They include carrying out the reaction in an ice bath, or by maintaining a sufficient distance between the tube and the surface of the substrate. However, as the use of an ice bath may not be sufficient and the size of the apparatus may make it impossible to place the delivery tube at an appropriate distance, an alternative is to dissolve the substrate in a suitable solvent, a fool-proof method that prevents this problem. While it does add the inconvenience of dealing with a solvent with some very volatile substrates, such as 2,3-dimethyl-2-butene, it is the best method. In addition to addressing volatility issues, bromination of this particular substrate should be carried out in the dark to avoid free radical allylic substitution. When either dichloromethane or ethyl acetate was used as the solvent, the resulting 2,3-dibromo-2,3-



dimethylbutane 8 was pure, according to GC-MS analysis, and was obtained in high yield.

Hybrid reaction design and accumulation of solvent in the delivery tube

As mentioned previously, to solve the above problems, we developed a hybrid PV-PTFE reaction design. A typical hybrid reaction set-up is shown in Fig. 8. Note that the bromine vapours flow directly into the solution and none leave the flask. Thus, the pressure-equalising arm can be left open. Alternatively, a partially inflated balloon can be attached to it.

While the hybrid reaction design addressed solvent uptake issues, occasionally the solvent vapours condensed and accumulated in the delivery tube (Fig. 9). While this affected neither the reaction outcome nor the yield, it required the use of an additional small excess (10-20%) of the reagent.

Except for the obvious way to avoid the accumulation of a solvent in the delivery tube, which is to carry out the reaction under solvent-free conditions, there are two principal ways



Fig. 8 Delivery of bromine to dicholormethane by means of a hybrid PV-PTFE reaction design. While the flow of bromine can be easily observed with a naked eye, it is difficult to see bromine vapour on a photograph. The reaction apparatus has been backlit and on the right the same photograph was contrast-enhanced to show the flow of bromine vapour.

Fig. 9 Accumulation of the solvent in the delivery tube. In this case, the reagent in the delivery tube was iodine monochloride and the solvent was dichloromethane (two different experiments shown).

to prevent this phenomenon. One is to utilise a less volatile solvent and another is to utilise a solvent that does not dissolve the reagent very well. For example, dichloromethane exhibited a tendency to accumulate in the delivery tube. It is both volatile and dissolves halogens efficiently. A change of solvent to ethyl acetate addressed the problem.

Delivery of the reagent out of the delivery tube at a high rate

The purpose of both hybrid and PV-PTFE reaction designs was to deliver either the neat reagent or the reagent in a solution at a controlled rate. However, sometimes the reagent was delivered at a rather fast rate and came out in droplets. Possible reasons for that are: (a) a drop of pressure in the reaction flask, (b) a build-up of pressure in the delivery tube, or (c) a combination of the two factors. Interestingly, this problem was observed only when the top of the delivery tube was completely sealed such as use of an inverted vial as a delivery tube (Figs 10a and b),²⁰ or a glass tube inserted into a rubber septum (Fig. 10c).

(a) When carrying reaction on neat volatile substrates, the formation of a non-volatile product lowers the pressure in the reaction vessel. This occasionally resulted in the draw of the reagent through the PTFE tape at a high rate. Instead of the preferred thin stream of vapour, the reagent was delivered dropwise (Fig. 10). Thus, the reagent was delivered at a faster rate than intended. An example is a solvent-free reaction of volatile liquid 2,3-dimethyl-2-butene **7** with bromine

to give a considerably less volatile solid 2,3-dibromo-2,3-dimethylbutane 8.

The problem could be solved by various means of pressure equalisation. One way is to place partially inflated balloons on both the reaction flask and the top of the tube. A better way is to equalise the pressure in the delivery tube and the reaction flask by connecting the top of the delivery tube with a side arm of the flask (Fig. 11). When a delivery vial is employed, the reagent adsorbed on a solid carrier such as silica should be used (see below).

(b) Build-up of pressure in the delivery vessel occurred when either a small vial or a glass tube inserted into a rubber septum was used along with a volatile reagent, such as bromine. Vapour accumulated in the upper part of the tube and exerted pressure on the liquid below forcing it out at a fast rate. Interestingly, when a stoppered delivery tube was used, no such fast delivery of the reagent was observed (Fig. 12).¹⁸ It is possible that the excess pressure was released by leaking at the stoppered joint.

(c) When a combination of both a drop in pressure in the reaction vessel and an increase of the pressure in the delivery tube occur, one can address them either by connecting the top of the delivery tube to a side arm of the reaction flask (Fig. 11), or by employing a reagent adsorbed on silica (see below).

Use of silica-adsorbed reagents

To make the reaction procedure safer and more environmentally friendly, we adsorbed the reagent on silica (Fig. 13). Strictly

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Fig. 10 Sometimes the reagent was delivered dropwise due to (a) and (b) the increased pressure in the delivery vessel (a 2-mL vial) and (c) the reduced pressure in the reaction flask. Bromination of (a) and (b) *trans*-stilbene and (c) 2,3-dimethyl-2-butene are shown.



Fig. 11 The best way to prevent the delivery of the reagent at a high rate is to equalise pressure by connecting the top of the delivery tube with the side arm of the reaction flask.

Fig. 12 Accumulated bromine vapour did not force bromine out of a stoppered delivery tube.



Fig. 13 Use of silica-supported reagent in hybrid PV-PTFE reaction. A, Silica was placed in a 2-mL vial; B, bromine was added; C, the vial was covered with PTFE tape and secured with an o-ring; D, the prepared vial can be capped and stored for future use; E, the vial was inserted into a rubber septum; F and G, the septum with the vial was inserted into the flask which contains the substrate dissolved in a suitable solvent.

speaking, this is no longer a phase-vanishing design as, in the course of the reaction, the silica phase does not vanish. Except for slightly longer reaction times there were no other differences in reaction outcomes compared to other PTFE reaction designs. The rate of the delivery of the reagent can be manipulated by

altering the reagent/silica ratio. At a high reagent/silica ratio (1:2), the reaction rate was very close to that of neat reagent. As the amount of reagent relative to silica was reduced, the rate of delivery was correspondingly slower. Upon completion of the reaction, silica can be reused. Used silica was extracted



Fig. 14 Examples of the use of silica-supported reagents in hybrid PV-PTFE reactions.



Fig. 15 When a reaction was carried out without stirring, there was some local accumulation of bromine. The white precipitate in the reaction on the left is *meso*-dibromostilbene.

with dichloromethane and analysed by means of GC-MS. We observed the presence of neither the substrate nor the reaction product in the extract.

The use of silica-supported bromine along with the substrate in a solution addressed all the problems associated with bromination of 2,3-dimethyl-2-butene (formation of the product on the surface of PTFE tape, fast dropwise draw of the reagent out of the delivery tube, and accumulation of the solvent in the delivery tube).

Examples are shown in Fig. 14. Note that this reaction design allows for a reaction to be carried out in a completely sealed vessel without any need for a pressure equalisation.

Local accumulation of the reagent

When a reaction was carried out without stirring, a local accumulation of the reagent was observed (Fig. 15). An obvious solution was to use a stirrer. However, we were concerned that the possible permeability of bulk PTFE coating and reaction of the reagent with the iron core may affect the outcome of longer experiments.²¹ Also, vigorous stirring sometimes resulted in the splattering of the delivery tube with the reaction mixture.

Even though the accumulation of the reagent was noticeable, there did not appear to be any effect on the reaction outcome in terms of yield and purity of the product. However, we carried out reactions on relatively simple systems where reactivity was very good (fast reaction rate) with few possibilities for competing side reactions and formation of by-products.

The use of a glass-coated stir-bar addressed the potential problem of the local accumulation of the reagent. If a glass-coated stir-bar is not available, one can be easily made from an iron bar (*e.g.* a nail) and a glass pipette.^{4,19}

Conclusion

We have examined potential complications and ways to address them in order to make PV-PTFE reactions a convenient and reproducible method. When designing a particular experiment one can anticipate potential obstacles by taking into account the nature of the reagent, the substrate and the solvent. A hybrid PV-PTFE reaction design combined with a silica-supported reagent successfully resolved most, if not all, of the problems we encountered so far. The method is particularly suitable for reactions involving volatile and highly reactive reagents. One also should keep in mind that, in some cases, a more traditional fluorous PV reaction, or simply a conventional reaction, may be more suitable.

Experimental

CAUTION: One must exercise care when handling bromine or iodine monochloride. Bromine and iodine monochloride are corrosive, cause skin burns, and their vapours are toxic. One should work in a fume hood and wear eye protection and gloves.

PTFE tape was commercially available Teflon tape (High Density PTFE tape, Mil. Spec. T-27730A) made by Taega Technologies purchased from Fisher Scientific (cat. No. 14-610-120)). All of the commercially available reagents (bromine, iodine monochloride, 2,3-dimethyl-2-butene, cis-stilbene, trans-stilbene, oxalyl chloride, hydrogen peroxide, rubrene, dichloromethane and ethyl acetate) were used as supplied without further purification. Dry dichloromethane was obtained from Aldrich and used without further purification. Commercially available 2,4-dinitrophenol was dissolved in dichloromethane, the solution was separated from water, dried over anhydrous MgSO₄, filtered and dichloromethane was removed under reduced pressure. The resulting 2,4-dinitrophenol was subjected one more time to the same drying procedure. GC-MS analyses were performed by means of an Agilent 6890N Gas Chromatograph equipped with an HP-5MS 30 m x 0.25 mm column and an Agilent 5973N MSD. All reaction products were characterized with no further purification, unless stated otherwise. Melting points were determined with a MEL-TEMP Electrothermal heater equipped with an alcohol thermometer and are uncorrected. Vials were National Scientific C4000-1 (clear) and C4000-2W (amber) 2-mL vials obtained from Fisher Scientific.

Preparation of halogen on silica reagent. In a 2-mL vial, silica (230–400 mesh, 1.00 g) was mixed with bromine or iodine monochloride (0.20 - 0.40 mL) of and left standing for 24 h before use.

meso-*Dibromostilbene* (2): A stir-bar, *trans*-stilbene 1 (0.450 g; 2.5 mmol) and ethyl acetate (15 mL) were placed into a 50-mL round bottom flask. A PTFE vial containing bromine adsorbed on silica was inserted (0.20 mL; 4.0 mmol of bromine; 1.0 g of silica) into the vapour phase above the solution. After 20 min the solid product was collected by vacuum filtration. *meso*-Dibromostilbene 2 (0.782 g) was isolated in 92% yield. The melting point was 237–237.5 °C (dec.) (lit.²⁵ 237–239 °C).

Bis(2,4-*dinitrophenyl*) *oxalate* (**4**): A stir-bar, dry 2,4-dinitrophenol **3** (0.368 g, 2.0 mmol) and dry dichloromethane (4.0 mL) were placed into a 10-mL round-bottom flask. The flask was cooled in an ice bath. A PTFE sealed tube filled with a solution of oxalyl chloride (0.095 mL, 1.10 mmol) in dichloromethane (0.5 mL) was inserted into the flask. The reaction was allowed to proceed until all of the oxalyl chloride solution had diffused into the vial (~10 min). The ice bath was removed

and stirring was continued for total of 30 min. Dichloromethane was removed under reduced pressure to give crude bis(2,4-dinitrophenyl) oxalate **4** (0.397 g, 94%). The product was used immediately in a chemiluminescence reaction.

d,l-Dibromostilbene (6): A stir-bar and *cis*-stilbene 5 (360 mg; 2 mmol) were placed in a 10-mL round-bottom flask. A PTFE sealed bromine tube was inserted into the flask and was kept inside until the colour of the bromine vapour persisted (15 min). The bromine delivery tube was replaced with a PTFE sealed tube filled with an aqueous paste of sodium thiosulfate until the colour of bromine vapour disappeared ($\sim 2-3$ min). A solid recovered from the flask contained considerable amounts of *meso*-dibromostilbene and *trans*-stilbene. Chromatography provided *d*,*l*-dibromostilbene 6 in a yield of 0.456 g (67%).

2,3-Dibromo-2,3-dimethylbutane (8): A stir-bar and neat 2,3-dimethyl-2-butene 7 (0.24 mL; 4.0 mmol) were added to a 50-mL round bottom flask. The flask was cooled in an ice bath and protected from the light. A septum containing a prepared vial of bromine was inserted into the flask. The reaction was allowed to proceed for 20 min. GC-MS analysis showed only a single peak due to 2,3-dibromo-2,3-dimethylbutane 8. A white solid was recrystallised from methanol to give 2,3-dibromo-2,3-dimethylbutane (0.803 g; 84%) yield. The melting point was 165–167 °C (lit.²⁶ 169–171 °C).

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