Video Article

Achieving Moderate Pressures in Sealed Vessels Using Dry Ice As a Solid CO_2 Source

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Abstract

Herein is presented a general strategy to perform reactions under mild to moderate CO_2 pressures with dry ice. This technique obviates the need for specialized equipment to achieve modest pressures, and can even be used to achieve higher pressures in more specialized equipment and sturdier reaction vessels. At the end of the reaction, the vials can be easily depressurized by opening at room temperature. In the present example CO_2 serves as both a putative directing group as well as a way to passivate amine substrates, thereby preventing oxidation during the organometallic reaction. In addition to being easily added, the directing group is also removed under vacuum, obviating the need for extensive purification to remove the directing group. This strategy allows the facile γ-C(sp^3)-H arylation of aliphatic amines and has the potential to be applied to a variety of other amine-based reactions.

Video Link

The video component of this article can be found at https://www.jove.com/video/58281/

Introduction

The use of gaseous compounds in chemical reactions typically requires specialized equipment and procedures[1,2]. At bench scale, some gases can be added directly from a tank using a high pressure regulator[3]. An alternative method is to condense the gas under cryogenic conditions[4,5]. Although useful, these strategies require the use of specialized pressure reactors with valves, which can be cost prohibitive for running numerous reactions in parallel. This can therefore greatly slow the rate at which reaction screening can proceed. As a result, chemists have found it desirable to introduce these compounds using alternative methods. Ammonia can be added to reactions using different ammonium carboxylate salts, taking advantage of the weak equilibrium between these salts and free ammonia[6]. Transfer hydrogenation is an important strategy for reduction reactions of olefins, carbonyl, and nitro groups that circumvents the use of flammable hydrogen gas with compounds such as ammonium formate or hydrazine as carriers of H_2[7]. Another gas of interest in this area is carbon monoxide[8] – CO can be generated *in situ* by liberation from metal carbonyl complexes[9,10], or alternatively it can be generated by decarbonylation from sources such as formates and formamides[11,12,13] or chloroform[14,15].

One gas which has not enjoyed significant development in this respect is carbon dioxide[16]. One reason for this is that many transformations that involve CO_2 also require high temperatures and pressures, and thus are automatically relegated to specialized reactors[17,18]. Recent efforts to develop more reactive catalysts, however, have facilitated running many of these reactions under atmospheric pressures of CO_2[19,20,21,22]. We recently discovered a reaction in which carbon dioxide could be used to mediate the γ-C(sp^3)–H arylation of aliphatic amines[23]. This strategy was expected to combine the benefits of a *static directing group* approach including amide[24,25,26,27,28], sulfonamide[29,30,31,32], thiocarbonyl[33,34], or hydrazone[35]-based directing groups (chemical robusticity), with the ease of a *transient directing group* (decreased step economy)[36,37,38,39].

Although the reaction could occur under atmospheric pressure of CO_2, the need for a Schlenk set-up to screen reactions proved prohibitively slow. Furthermore, increasing the pressure slightly led to improved reaction yields, but could not be easily achieved using a Schlenk line. We therefore sought an alternative strategy, and subsequently identified that dry ice could be easily used as a solid source of CO_2 that could be added to a variety of reaction vessels to introduce the necessary amount of carbon dioxide to achieve moderate pressures (**Figure 1**). Though underutilized in synthesis, a similar strategy is fairly common as a method to generate liquid CO_2 for chromatography and extraction applications[40,41,42,43,44]. Utilizing this strategy allowed our group to rapidly screen large numbers of reactions in parallel, while the ability to access moderate CO_2 pressures of between 2-20 atmospheres were critical to improving the yields of the reactions. Under these conditions, both primary (1°) and secondary (2°) amines can be arylated with electron rich and electron poor aryl halides.

Protocol

CAUTION: 1) The following protocols have been deemed safe through repeated trials. However, caution should be exercised when sealing vials, throughout the reaction, and especially when opening the reactions, as inhomogeneity in the reaction vials may lead to equipment failure. Vials should be inspected for physical defects prior to use. Vials should be placed behind some form of blast shield or hood sash immediately after sealing to prevent incidents should the vials fail. 2) Although there is little chance for asphyxiation due to the small quantities of CO_2 used, reactions should be set-up as well as opened in a well-ventilated area or in a fume hood. 3) Dry ice is a cryogen and can cause serious tissue damage. Care should therefore be exercised while manipulating it to avoid frostbite, such as limiting direct contact or using cryogenic gloves. 4) Dry ice will condense water vapor, meaning that prior to use, the dry ice should be mechanically exfoliated to ensure the mass is of $CO_{2(s)}$ only. This can be achieved by simply rubbing the dry ice between one's fingers, or more safely, rubbing it between one's fingers with a protective layer such as a glove or towel.

1. Reaction in a 7.5 mL Vial (Air Not Excluded)

1. Add a stir bar to a dry 7.5 mL vial.
2. Add palladium acetate (6.7 mg, 0.03 mmol) to the vial.
3. Add silver trifluoroacetate (99.9 mg, 0.45 mmol) to the vial.
4. Add phenyl iodide (92.3 mg, 0.45 mmol) to the vial.
5. Add *tert*-amyl amine (26.3 mg, 0.30 mmol) to the vial.
6. Add acetic acid (1.0 mL) to the vial.
   Note: The ratio of solution volume to vial size is important, as the immediate sublimation of CO_2 upon addition of dry ice can mechanically displace solvent if too much is used relative to the size of the reaction vessel.
7. Add deionized water (21.7 µL, 12.1 mmol) to the vial.
8. Weigh dry ice (26.3 mg, 0.60 mmol), and *immediately* add the dry ice to the vial, while ensuring to also *immediately* seal the vial with a PTFE-lined cap.
   Note: The whole operation should be performed within approximately 5 seconds to prevent sublimation and escape of the small amount of CO_2 added (this is slowed by the formation of frozen acetic acid around the dry ice). The amount of CO_2 added will be an approximate value, and in our hands a deviation of a few mg is permissible.
9. Stir the sealed reaction vial for 15 minutes at room temperature.
10. Transfer the reaction vessel to a pre-heated plate at 110 °C and stir for 14 hours before allowing to cool.
11. Upon cooling, carefully open the vial to vent CO_2.
12. Remove all of the volatiles *in vacuo*.
    Note: This operation can be performed in the vial, or the solution can be transferred to a larger round bottom flask.
13. Add 1.2 M $HCl_{(aq)}$ (6 mL) to the reaction mixture and stir open to air for 15 minutes.
14. Transfer the aqueous fraction to a separatory funnel, washing with additional 1.2 M HCl (4 mL), and extract with a 1:1 diethyl ether/hexanes mixture (3 x 8 mL).
    Note: This organic wash contains excess phenyl iodide and other neutral by-products, and can be disposed of.
15. Neutralize and make basic the aqueous solution by addition of saturated $NH_4OH_{(aq)}$ (10 mL is a good starting point).
16. Extract the aqueous layer with dichloromethane (2 x 10 mL).
17. Dry the combined organic fractions over Na_2SO_4, then filter into a tared sample vial.
18. Evaporate the solvent *in vacuo*, giving the product (2-Methyl-4-phenyl-butanamine) as a yellow oil.

2. Reaction in a 7.5 mL Vial (Purging Conditions – Air Excluded)

1. Add a stir bar to a dry 7.5 mL vial.
2. Add palladium acetate (6.7 mg, 0.03 mmol) to the vial.
3. Add silver trifluoroacetate (99.9 mg, 0.45 mmol) to the vial.
4. Add phenyl iodide (92.3 mg, 0.45 mmol) to the vial.
5. Add *tert*-amyl amine (26.3 mg, 0.30 mmol) to the vial.
6. Add acetic acid (1.0 mL) to the vial.
   Note: The ratio of solution volume to vial size is important, as the immediate sublimation of CO_2 upon addition of dry ice can mechanically displace solvent if too much is used relative to the size of the reaction vessel.
7. Add deionized water (21.7 µL, 12.1 mmol) to the vial.
8. Tare the vial on a balance, add approximately 98 mg of dry ice, and then allow the CO_2 to sublimate off until a final mass of approximately 26 mg is achieved, followed by *immediately* sealing the vial with a PTFE-lined cap.
   Note: If desirable, this step can be performed with a greater mass of dry ice to further exclude air from the vial. It is noteworthy that this may introduce water, and thus may not be the most effective strategy for water sensitive reactions.
9. Stir the sealed reaction vial for 15 minutes at room temperature.
10. Transfer the reaction vessel to a pre-heated plate at 110 °C and stir for 14 hours before allowing to cool.
11. Upon cooling, carefully open the vial to vent CO_2.
12. Remove all of the volatiles *in vacuo*.
    Note: This operation can be performed in the vial, or the solution can be transferred to a larger round bottom flask.
13. Add 1.2 M $HCl_{(aq)}$ (6 mL) to the reaction mixture, and stir open to air for 15 minutes.
14. Transfer the aqueous fraction to a separatory funnel, washing with additional 1.2 M HCl (4 mL), and extract with a 1:1 diethyl ether/hexanes mixture (3 x 8 mL).
    Note: This organic wash contains excess phenyl iodide and other neutral by-products, and can be disposed of.
15. Neutralize and make basic the aqueous solution by addition of saturated $NH_4OH_{(aq)}$ (10 mL is a good starting point).

16. Extract the aqueous layer with dichloromethane (2 x 10 mL).
17. Dry the combined organic fractions over Na_2SO_4, then filter into a tared sample vial.
18. Evaporate the solvent in vacuo, giving the product (2-Methyl-4-phenyl-butanamine) as a yellow oil.

3. Reaction in a 40 mL Vial (Air Not Excluded)

1. Add a stir bar to a dry 40 mL vial.
2. Add palladium acetate (33.5 mg, 0.15 mmol) to the vial.
3. Add silver trifluoroacetate (499.5 mg, 2.25 mmol) to the vial.
4. Add phenyl iodide (461.5 mg, 2.25 mmol) to the vial.
5. Add tert-amyl amine (131.5 mg, 1.5 mmol) to the vial.
6. Add acetic acid (5.0 mL) to the vial.
   Note: The ratio of solution volume to vial size is important, as the immediate sublimation of CO_2 upon addition of dry ice can mechanically displace solvent if too much is used relative to the size of the reaction vessel.
7. Add deionized water (108.5 µL, 6.02 mmol) to the vial.
8. Weigh dry ice (131.5 mg, 3.0 mmol), and immediately add the dry ice to the vial, while ensuring to also immediately seal the vial with a PTFE-lined cap.
   Note: The whole operation should be performed within approximately 5 seconds to prevent sublimation and escape of the small amount of CO_2 added (this is slowed by the formation of frozen acetic acid around the dry ice). The amount of CO_2 added will be an approximate value, and in our hands a deviation of a few mg is permissible.
9. Stir the sealed reaction vial for 15 minutes at room temperature.
10. Transfer the reaction vessel to a pre-heated plate at 110 °C and stir for 14 hours before allowing to cool.
11. Upon cooling, carefully open the vial to vent CO_2.
12. Remove all of the volatiles *in vacuo*.
    Note: This operation can be performed in the vial, or the solution can be transferred to a larger round bottom flask.
13. Add 1.2 M $HCl_{(aq)}$ (30 mL) to the reaction mixture and stir open to air for 15 minutes.
14. Transfer the aqueous fraction to a separatory funnel, washing with additional 1.2 M HCl (20 mL), and extract with a 1:1 diethyl ether/hexanes mixture (3 x 8 mL).
    Note: This organic wash contains excess phenyl iodide and other neutral by-products, and can be disposed of.
15. Neutralize and make basic the aqueous solution by addition of saturated $NH_4OH_{(aq)}$ (10 mL is a good starting point).
16. Extract the aqueous layer with dichloromethane (2 x 20 mL).
17. Dry the combined organic fractions over Na_2SO_4, then filter into a tared sample vial.
18. Evaporate the solvent *in vacuo*, giving the product (2-Methyl-4-phenyl-butanamine) as a yellow oil.

4. Reaction in a 35 mL Pressure Tube (Air not excluded)

1. Add a stir bar to a dry 35 mL pressure tube.
2. Add palladium acetate (6.7 mg, 0.03 mmol) to the pressure tube.
3. Add silver trifluoroacetate (132.5 mg, 0.6 mmol) to the pressure tube.
4. Add phenyl iodide (183.6 mg, 0.9 mmol) to the pressure tube.
5. Add 2-methyl-*N*-(3-methylbenzyl)butan-2-amine (57.4 mg, 0.3 mmol) to the pressure tube.
6. Add acetic acid (1.0 mL) to the vial, followed by 1,1,1,3,3,3,-hexafluoroisopropanol (1.0 mL).
   Note: The ratio of solution volume to vial size is important, as the immediate sublimation of CO_2 upon addition of dry ice can mechanically displace solvent if too much is used relative to the size of the reaction vessel.
7. Add deionized water (21.7 µL, 1.2 mmol) to the pressure tube.
8. Weigh dry ice (1.32 g, 30 mmol), and *immediately* add the dry ice to the pressure tube, while ensuring to also *immediately* seal the pressure tube with the appropriate Teflon screw cap.
   Note: The whole operation should be performed within approximately 5 seconds to prevent sublimation and escape of the small amount of CO_2 added (this is slowed by the formation of frozen acetic acid around the dry ice). The amount of CO_2 added will be an approximate value, and in our hands a deviation of a few mg is permissible.
9. Stir the sealed reaction vessel for 15 minutes at room temperature.
10. Transfer the reaction vessel to a pre-heated plate at 90 °C and stir for 24 hours before allowing to cool.
11. Upon cooling, put a towel or padded glove over the cap, and carefully open the pressure tube to vent CO_2.
12. Remove all of the volatiles *in vacuo*.
    Note: This operation can be performed in the pressure tube with an appropriate adaptor, or the solution can be transferred to a larger round bottom flask.
13. Add 1.2 M $HCl_{(aq)}$ (12 mL) to the reaction mixture and stir open to air for 15 minutes.
14. Transfer the aqueous fraction to a separatory funnel, washing with additional 1.2 M HCl (8 mL), and extract with a 1:1 diethyl ether/hexanes mixture (3 x 8 mL).
    Note: This organic wash contains excess phenyl iodide and other neutral by-products and can be disposed of.
15. Neutralize and make basic the aqueous solution by addition of saturated $NH_4OH_{(aq)}$ (10 mL is a good starting point).
16. Extract the aqueous layer with dichloromethane (2 x 10 mL).
17. Dry the combined organic fractions over Na_2SO_4, then filter into a tared sample vial.
18. Evaporate the solvent *in vacuo*, giving the product (2-Methyl-N-(3-methylbenzyl)-4-phenylbutan-2-amine) as a yellow oil.

Representative Results

Following these protocols, it is possible to charge a reaction vial with an appropriate amount of carbon dioxide to achieve chemical reactions that require CO_2 atmospheres. The pressure achieved in Step 1 is calculated to be approximately 3 atmospheres (see discussion for determination of this value), although due to partial solvation, the observed pressure is in the vicinity of 2 atmospheres at room temperature, and should be approximately 2.6 atmospheres under the reaction conditions. Therefore, under the conditions in Step 1, 2-Methyl-4-phenyl-butanamine can be obtained in 69% yield (**Figure 2**). By first purging the flask of air through displacement by sublimating CO_2 (Step 2), the yield can be increased slightly to 72%. To distinguish between these results at ~2.6 atmospheres of pressure, performing the reaction under 1 atmosphere of CO_2 using a standard Schlenk set-up furnishes the desired product in only 49% isolated yield. If no CO_2 is used, or the vial is not properly sealed and thus a stable CO_2 atmosphere is not maintained, then <5% yield of the desired product is detected by ^{1}H NMR (using 1,1,2,2-tetrachloroethane as reference standard). Meanwhile, scaling the reaction up by a factor of 5 while simultaneously using a larger reaction vial (Step 3) can still give product, albeit in a slightly decreased yield of 42%. The reactions can also be performed in pressure reaction tubes (**Figure 1**), in this case allowing the synthesis of 2-Methyl-*N*-(3-methylbenzyl)-4-phenylbutan-2-amine in 40% yield (**Figure 3**).

Figure 1. Reaction Vessels Used in this Study. From left to right: 2 dram Vial, 10 Dram Vial, 35 mL Pressure Tube). Please click here to view a larger version of this figure.

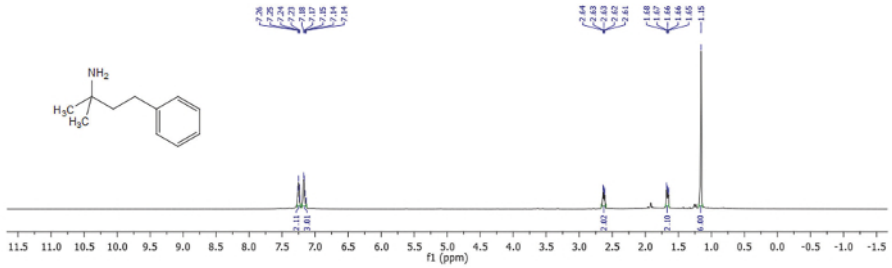

Figure 2. ^{1}H NMR of 2-Methyl-4-phenyl-butanamine. 400 MHz, $CDCl_3$, 298 K. Please click here to view a larger version of this figure.

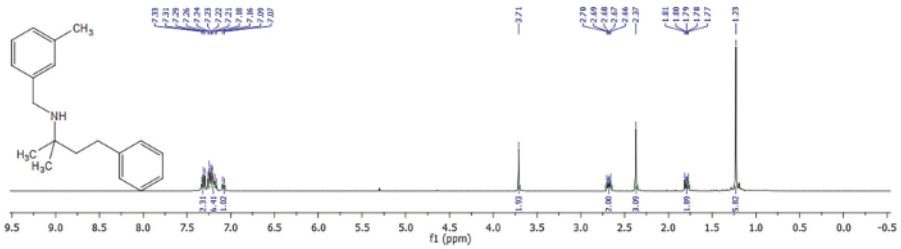

Figure 3. ^{1}H NMR of 2-Methyl-*N*-(3-methylbenzyl)-4-phenylbutan-2-amine. 400 MHz, $CDCl_3$, 298 K. Please click here to view a larger version of this figure.

					Carbon Dioxide Loading in Empty Vials						
		100 mg	125 mg	150 mg	175 mg	200 mg	225 mg	250 mg	275 mg	300 mg	Legend
	25ºC	√	√	√	√	√	√	√	√	√	√ = Stable Under Conditions
	60ºC	√	√	√	√	√	√	√	√	√	x = Unstable Under Conditions
	70ºC	√	√	√	√	√	√	√	√	√	
	80ºC	√	√	√	√	√	√	√	√	√	
	90ºC	√	√	√	√	√	√	√	√	√	
Temperature	100ºC	√	√	√	√	√	√	√	√	√	
	110ºC	√	√	√	√	√	√	√	√	√	
	120ºC	√	√	√	√	√	√	√	√	√	
	130ºC	√	√	√	√	√	√	√	√	√	
	140ºC	√	√	√	√	√	√	√	√	√	
	150ºC	√	√	√	√	√	√	√	√	√	
	160ºC	√	√	√	√	√	√	√	√	√	

Table 1. Relative Stability of 7.5 mL Vials Based on CO_2 Loading and Temperature. Vials were loaded with the requisite amount of dry ice, followed by immediately sealing with a PTFE-lined cap. The vials were immediately placed into Pie-blocks behind a blast shield in a fumehood, followed by heating to 60 °C, followed by raising 10 °C every hour to a peak of 160 °C. The vials were then cooled, and opened carefully to confirm no loss of CO_2 pressure had occurred.

					Carbon Dioxide Loading in Empty Vials							
		300 mg	325 mg	350 mg	375 mg	400 mg	425 mg	450 mg	475 mg	500 mg	525 mg	Legend
	25ºC	√	√	√	√	√	√	√	√	√	x	√ = Stable Under Conditions
	60ºC	√	√	√	√	√	√	√	√	√	x	x = Unstable Under Conditions
	70ºC	√	√	√	√	√	√	√	√	√	x	
	80ºC	√	√	√	√	√	√	√	√	√	x	
	90ºC	√	√	√	√	√	√	√	√	√	x	
Temperature	100ºC	√	√	√	√	√	√	√	√	√	x	
	110ºC	√	√	√	√	√	√	√	√	√	x	
	120ºC	√	√	√	√	√	√	√	√	√	x	
	130ºC	√	√	√	√	√	√	√	√	√	x	
	140ºC	√	√	√	√	√	√	√	√	√	x	
	150ºC	√	√	√	√	√	√	√	√	√	x	
	160ºC	√	√	√	√	√	√	√	√	√	x	

Table 2. Relative Stability of 40 mL Vials Based on CO_2 Loading and Temperature. Vials were loaded with the requisite amount of dry ice, followed by immediately sealing with a PTFE-lined cap. The vials were immediately placed into Pie-blocks behind a blast shield in a fumehood, followed by heating to 60 °C, followed by raising 10 °C every hour to a peak of 160 °C. The vials were then cooled, and opened carefully to confirm no loss of CO_2 pressure had occurred.

Discussion

Using the van der Waals Equation of State, the approximate pressure of these systems can be calculated[45]

Eq. 1: $$\left[P + a\left(\frac{n}{V}\right)^2\right]\left(\frac{V}{n}\right) - b = RT \rightarrow P = \frac{nRT}{(V-nb)} - \frac{n^2 a}{V^2}$$

Under the conditions in Protocol 1, we can assume 26.3 mg of CO_2 gives n =5.98 x 10^{-4} mols

$$P = \frac{5.98\ x\ 10^{-4} mols * 8.314\ m^3 PaK^{-1} mols^{-1} * 383\ ^{\circ}K}{(6.5\ x\ 10^{-6} m^3 - 5.98\ x\ 10^{-4} mols * 4.269\ x\ 10^{-7} m^3 mols^{-1})} - \frac{5.98\ x\ 10^{-4} mols^2 * 3.96\ x\ 10^{-1} Pa\ m^6}{(6.5\ x\ 10^{-6} m^3)^2} = 2.91\ x\ 10^2\ kPa$$

As a rough estimate, this suggests that in Protocol 1 the reactions were performed under approximately 2.8 atmospheres of CO_2. Assuming negligible displacement of the native atmosphere in the vessel (as noted above, a patina of frozen acetic acid will slow the initial sublimation of the dry ice, facilitating better accuracy in the measurement of added dry ice), however, the total pressure would then be expected to be modeled better by Dalton's law:

Eq. 2: $$p_{total} = p_{native} + p_{CO_2}$$

$$p = 1\ atm + 2.8\ atm = 3.8\ atm$$

This model does not take into account that some of the gases will be dissolved in the solvent. In that case, it was necessary to attach a pressure gauge to adequately assess the pressure. By attaching a septum to the vial and inserting a pressure gauge, it was possible to measure the pressure at room temperature. The observed pressures over multiple reactions were only 15 ± 3 psi above atmospheric pressure (≈ 1 ± 0.2 atmospheres), or around 2 atmospheres total. Although the Henry constant of CO_2 in neat acetic acid was not readily available for comparison, it is known that addition of acetic acid to water improves the solubility of carbon dioxide[46]. The estimated pressure at room temperature could be calculated using the previous approach:

$$P = \frac{5.98\ x\ 10^{-4} mols * 8.314\ m^3 PaK^{-1} mols^{-1} * 298\ ^{\circ}K}{(6.5\ x\ 10^{-6} m^3 - 5.98\ x\ 10^{-4} mols * 4.269\ x\ 10^{-7} m^3 mols^{-1})} - \frac{5.98\ x\ 10^{-4} mols^2 * 3.96\ x\ 10^{-1} Pa\ m^6}{(6.5\ x\ 10^{-6} m^3)^2} = 2.28\ x\ 10^2\ kPa$$

$$p = 1\ atm + 2.3\ atm = 3.3\ atm$$

The expected pressure would therefore be a slightly lower 3.3 atmospheres at room temperature in the absence of gas dissolving in the solvent. The difference between the observed and calculated pressures imply that CO_2 has relatively high solubility in the organic solvent. Assuming

negligible difference in the amount of dissolved CO_2 over the temperature range, an increase in temperature from 298 K to the reaction temperature of 383 K would increase the pressure within the 2 dram vial to ~2.6 atmospheres.

To adequately assess the practical operating conditions, 2 dram vials were set-up with varying amounts of CO_2, followed by screening these at different temperatures. To ensure operator safety, the vials were only heated *after* being placed behind a blast shield to contain any vial failures. If the vials blew up, the conditions were considered too harsh for the vials. Through these experiments it was determined that CO_2 loading of up to 200 mg was tolerated at 110 °C for the 2 dram (7.5 mL) vials through consistent trials. This corresponds to approximately 20.7 atmospheres of pressure based on the previous approach, not withstanding the amount of gas dissolved, which may decrease the total pressure by a few atmospheres. Beyond 200 mg loading, however, the reaction vials would generally explode before reaching the target temperature of 110 °C. Caution should be exercised when modifying the conditions, however: In one scenario a related reaction was attempted at 160 °C with only 150 mg of CO_2, but the vial failed before it had reached the target temperature. The greatest danger for modifying the reaction conditions would be from increasing the loading of CO_2, as this can cause the vials to fail *before* safe engineering controls, such as blast shields, can be implemented.

A potential limitation to this strategy is the lack of data about the stability of the vials under different conditions. Therefore, it was necessary to screen the vials for their ability to withstand different pressures under a range of different temperatures. This was initiated with the 7.5 mL vials (**Table 1**). Each vial was charged with a pre-determined quantity of dry ice, followed by immediate sealing with a PTFE-lined screw cap. These vials were observed to be tolerant of these conditions, and none failed at room temperature. The temperature was then raised for all of the vials, and no explosions occurred during the experiment. Upon cooling, each vial was opened to confirm they had maintained pressurization with CO_2. This suggests that the vials can tolerate upwards of 26.5 atmospheres of pressure, which is in contrast to the reaction conditions in which ~20.7 atmospheres of pressure was the consistent limit. It is therefore encouraged that solvent identity and volume be carefully considered in deviation from the disclosed method.

A similar screen for maximum tolerance was performed using 40 mL reaction vials (**Table 2**). In this case, an upper limit for the CO_2 loading of *empty vials* was determined to be 500 mg. Above this the vials quickly failed at room temperature. Surprisingly, the calculated pressure of the samples that began to fail at room temperature was approximately 7 atmospheres and above. This is in contrast to the vial containing 500 mg of CO_2, which was stable at 160 °C, which would correspond to a calculated pressure of just under 10.5 atmospheres. These results were reproducible across different vials, but there is no clear explanation for this phenomenon at this time. Under the conditions described under Protocol 3, only approximately 300 mg loadings of CO_2 were tolerated. However, this is actually in line with the previous experiments, as under the conditions the pressure, uncorrected for potential absorption of carbon dioxide by the solvent, would be approximately 10 atmospheres. The decreased stability of the larger vials to pressure is expected, and suggests that these procedures are better performed in vessels that have smaller diameters and thicker walls[47].

In summary, this protocol for using dry ice as a solid CO_2 source in readily available glassware is expected to open new directions in the field of synthetic chemistry. By generating low to moderate pressures inside of sealed vials or pressure tubes, carbon dioxide fixation processes such as carboxylation[48,49,50], as well as CO_2 reduction[51,52,53], can be achieved without the use of expensive specialized equipment. This newly adopted strategy will facilitate advances in the area of valorization of CO_2 by incorporation into useful chemical feedstocks such as cyclic carbonates, poly carbonates, and carbamates[54]. Furthermore, the strategy of introducing CO_2 as a solid may also be beneficial where mixtures of gases are desired, such as CO_2 and CO, or CO_2 and H_2, as this facilitates the addition of both reagents in a non-gaseous form. Although use of dry ice to introduce liquid CO_2 has been used for extractions and chromatography[40,41,42,43,44], this protocol for introducing CO_2 as a solid may also be useful for *in situ* generation of $CO_{2(L)}$ for use as a reaction solvent[55,56,57], Future work exploring other uses for this approach, especially the combination of CO_2 with other gas-precursors, are currently underway in our group.

Disclosures

The use of CO_2 as a directing group for C-H activation of Lewis basic substrates is currently the focus of United States Provisional Patent #62/608,074.

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