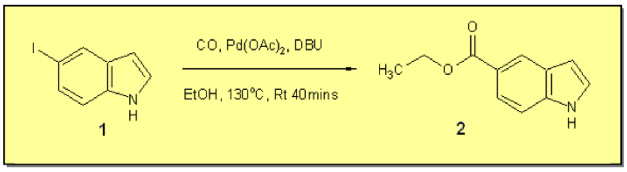
Application Note 20:

Reaction Optimization and Scale-Up of an Ethxycarbonylation Reaction of Unprotected Iodoindole with Carbonmonoxide Gas

Produced by Vapourtec

Abstract

This example illustrates the use of the new Vapourtec tube in tube gas reactor combined with the Vapourtec R-Series system to react reagent gases under pressure without the use of scale limiting pressure reactors (e.g. Parr 'bombs'). Here we describe the catalytic ethoxycarbonylation of unprotected iodoindole with CO gas.



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Background

It is well known that palladium catalyzed C-C coupling reactions of aryl halides are a powerful tool in organic synthesis to functionalize aromatic rings but Pd catalyzed carbonylations of aryl halides are relatively under used. There are very few examples at all of Pd-catalyzed reactions of unprotected haloindoles probably due to the relatively acidic NH proton and the possibility of polymerization under these conditions.

These reactions offer the specific, selective synthesis of a number of carboxylic acid derivatives accessing acids, esters, amides, aldehydes and ketones by reacting the aryl halide, CO and the corresponding nucleophile.

The use of carbon monoxide gas however requires a high level of safety precautions due to its toxicity and highly flammable nature and the use of specific volume limiting high pressure vessels. The application of flow chemistry to limit the reaction volume and the continuous replenishment of the reactants offers several advantages here as we are able to reduce the overall volume of CO in the system.

Further limitations of traditional batch methods for these reactions are the long reaction times, typical 12-24 hrs. We show here how using flow conditions can significantly reduce these times while running at relatively high concentrations.

We describe here the use of the Vapourtec "Tube-in-Tube" gas/liquid reactor to continuously feed the carbon monoxide gas into the reaction as it is consumed. Liquid is fed through the coil just like any other Vapourtec reactor, but there is also a connection for gas which is fed at the desired pressure from a pressure regulated supply.

The reactor is compatible with all existing R4 heater modules. When it is used in conjunction with the R4, the reactor's temperature can be controlled between ambient and 150 °C, a facility not available with some competing tube-in-tube systems.

Method (Optimization)

Note that guidance for safe use of the Vapourtec gas/liquid reactor can be found in the document Using The Vapourtec Gas Reactor which is available from Vapourtec on request.

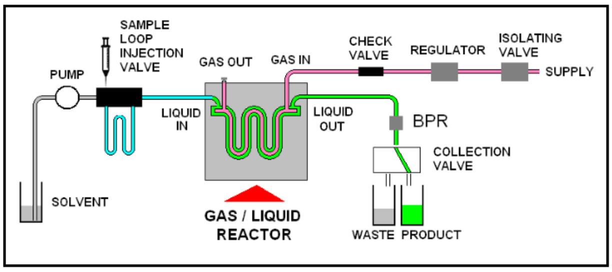


Figure 1. Representative setup

Using Flow Control Software

At time of writing there is not yet support for the gas reactor in flow control software as a specific reactor type.

There is also a manual startup sequence for the gas reactor which must be followed, which is outlined below.

Furthermore, the flow control software dispersion algorithm has not yet been calibrated for use with the gas reactor.

Setup

The flow reactor was configured using a combination of the R2 Plus pump module and R4 reactor module as shown in Figs 1, 2. Only one liquid input stream was connected as the second reactant (CO) was continuously introduced through the gas permeable membrane.

A 15 mL gas/liquid tube-in-tube reactor was installed along with a Vapourtec acid resistant BPR (back pressure regulator) fitted in-line between the reactor outflow and the collection valve. At this stage, a single 2 ml sample loop was used to limit the amount of material used for reaction optimization.

A stock solution was prepared;

A stock solution of the reagents was prepared;

Solution A

- 1.0 M of the substrate 1 (Aldrich 563838, CAS 16066-91-4) in DCM,
- 1,8-diazabicyclo[5.4.0]undec-7-ene,
- DBU 1.1 eq (Aldrich 139009, CAS 6674-22-2),
- Pd(OAc)2 5 mol% (Aldrich 520764, CAS 3375-31-3).

The pressure regulated CO stream was introduced via the gas input of the reactor and was supplied continuously throughout the experiment. The collection valve 'Collect' output was directed into 20 mL glass vials.

System solvent:	EtOH
Reagent A:	1.0 M substrate 1 (10 mmol) in EtOH (10 mL), DBU 1.1eq, Pd(OAc)2 5 mol%
Reagent B:	30 bar CO(g)
Flow rate A:	variable (500 µL/min)
Reactor volume:	15 mL gas/liquid reactor
Reactor temperature:	130 °C
Back pressure regulator:	25 bar. Acid resistant bpr used with 1 mm bore throughout.

Sequence of Activities

It is important that the procedure for running the gas/liquid reactor (as described in **Using The Vapourtec Gas Reactor**) is carried out to prolong the life of the reactor and to obtain reproducible results. The differential pressure between the gas supply and the system liquid pressure should be maintained within recommended limits.

A back pressure regulator value was chosen such that the system liquid pressure at operating conditions would be approximately equal to the intended gas pressure, thus ensuring that the differential between the two pressures would be minimized.

To "start the reactor up" the following steps were followed

- set gas pressure to the target value by turning up the regulator.
- purge the gas cavity by unscrewing the "gas out" plug just enough to release the pressure, allowing any accumulated solvent vapor to be vented. After 5 seconds re-seal the plug.
- set the R2 pump module trip pressure appropriately to ensure liquid pressure could not exceed the maximum value for the reactor.
- With the BPR disconnected from the output and the selection valve set to solvent, set the pump flow rate to 2.5 mls / min and leave at that level until all the air had been pumped out of the reactor
- Turn flow off, replace the BPR , and set the flow to 0.5 ml/min. Wait for the pressure to rise to the target. At this point, check for leaks.

Before running reactions, sample loop A was primed with system solvent (EtOH) with these steps

- Set channel A selection valve to solvent
- Set channel A injection valve to 'inject'
- Set pump A to run at 1.0 mL/min for 5mins

Then the following sequence of events was carried out for each reaction

- Set pump A to 0.5 ml/min
- Set target temperature for reactor
- Load sample loop A with reagents
  a. set injection valve A to 'Load'
  b. inject the desired solution via the rheodyne valve input (ensuring excess can be seen exiting the waste valve)
- Wait for the reactor to reach target temperature
- Set flow rate on pump A to achieve target residence time
- Set injection valve A to 'Inject'

- Use collection valve to collect product at appropriate time

Optimization experiments were carried out with this reaction to determine the best reaction conditions and to determine the minimum catalyst loading to facilitate a complete reaction.

The following parameters were varied:

- choice of base
- temperature
- residence time
- gas pressure

There is little in the way of published literature examples of homogeneous catalytic systems for these transformations probably due to the increased reactivity of heterogeneous catalytic systems. Another concern was further limiting the reactivity of any homogeneous system with chelating ligands and bases to aid in solubilizing our palladium source.

However, initial observations and development of conditions from earlier work (see Vapourtec application note 19) suggested a good place to start was with low loadings of palladium acetate(0.5 mol%) in EtOH at high temperatures (100 – 150 °C) with DBU (1.1 eq) as the base.

Results (initial optimization)

Our initial experiment using the stock solution of 5-iodoindole, DBU and Pd(OAc)2 at 130 °C, 30 min residence time and 30 bar CO gave us a quantitative conversion by LCMS. We then ran a short series of experiments to determine whether we could reduce the residence time (reaction time) to potentially increase the mass transfer of the reaction. As shown in table 1 there was little difference in the relative purity of the desired ethoxy ester from 5 mins to 30 mins residence time under these conditions.

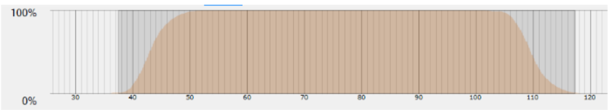
Entry	Conc [M]	Temp (°C)	Flow A (µl/min)	Residence Time (min)	Base	CO (bar)	$Pd(OAc)_2$ (mol%)	% Purity by HPLC	
								Product	SM
1	1	130	500	30	DBU	30	0.5	100	0
2	1	130	750	20	DBU	30	0.5	100	0
3	1	130	1500	10	DBU	30	0.5	96	4
4	1	130	3000	5	DBU	30	0.5	93	7

Table 1. Optimization of Ethoxycarbonylation of 5-Iodoindole.

Dispersion

It is to be highlighted that these results were obtained by introducing a 2 ml aliquot of the reaction mixture via the injection loop into a 15ml reactor.

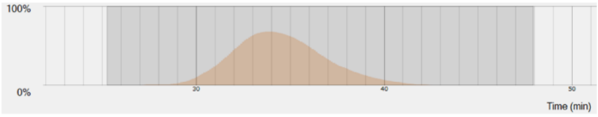
When a "plug" of reaction mixture passes through a series of tubes, there is dispersion which make the leading and trailing edge of the plug less well defined. Therefore the concentration of reagents (as opposed to system solvent) does not rise immediately to 100% as the leading edge arrives at the collection point.



Reagent concentration as observed at the collection point.

It is ideal to base analysis on the steady state part of the collected output, as this gives data which is directly representative of future scaleup. In the steady state part of the collection window, reagent concentration is representative of the original reagent supply.

If, however, the amount of reagent used is small, the effect of dispersion may be to prevent the output ever reaching a steady state, even for a moment. (See below)



Reagent concentration when aliquot size is small relative to dispersion

This means that the reaction concentration in the reactor never actually reaches that of the reagent supplied to the process.

In the optimization described so far, this was the case, as the plug used (2 ml) was small compared with the length of the total reactor flowpath.

Before proceeding to any significant scaleup, therefore, it is necessary to generate conditions for a larger slug that reaches steady state at least for a short period.

Method (Optimization - Steady State Conditions)

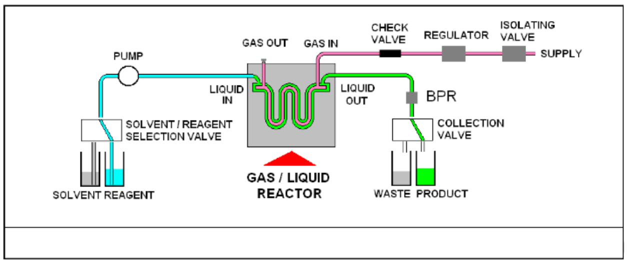
As described the optimum reaction conditions for reacting a dispersed 2 ml aliquot were 150 °C, for 5 mins at 30 bar CO pressure. It was decided to then investigate the effect of running these conditions on a reaction that had reached steady state and would therefore be at the original concentration of [1.0] M.

Previous similar work (See Vapourtec application note 19) running conditions developed for small aliquots at larger scale had shown that a 5 min residence time was unlikely to give a high conversion to the desired compound. Instead of increasing the residence time in steps a 40 min residence time was tried immediately. Under these reaction conditions a continuous run was carried out to calculate an isolated yield and to obtain full characterization of the product. Aliquots were taken over three points in the steady state output from the, diluted with

Setup:

System solvent:	EtOH
Reagent A:	1.0 M substrate 1 (25 mmol) in EtOH (25 mL), DBU 1.1eq, Pd(OAc)2 0.5mol%
Reagent B:	30 bar CO(g)
Flow rate A:	375 µL/min
Reactor volume:	15 mL gas/liquid reactor
Reactor temperature:	130°C
Back pressure regulator:	25 bar. Acid resistant BPR used with 1mm bore throughout.
Residency time:	40 minutes

The configuration was altered from the screening reactions. The sample loop was by-passed with solution A introduced directly through the pump.



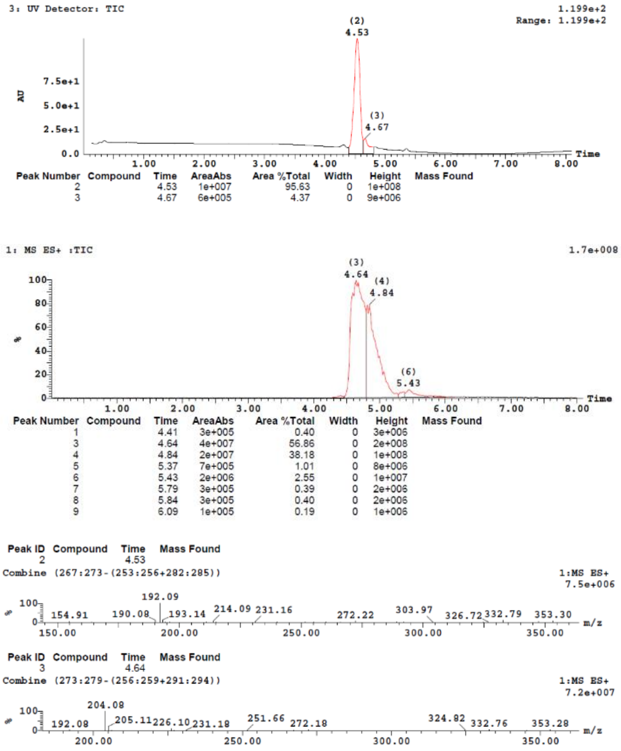
The procedure for setting up the gas reactor is repeated from that described for the optimization experiments.

The following sequence of events was carried out for each reaction

- Set channel A solvent/reagent selection valve to solvent
- Set pump A to 0.5 ml/min
- Set target temperature for reactor

- Wait for the reactor to reach target temperature
- Set flow rate on pump A to achieve target residence time
- Set channel A solvent/reagent selection valve to reagent
- Wait until 25 ml of reagent has been pumped (time calculated based on flow rate)
- Set channel A solvent/reagent selection valve to solvent
- Use collection valve to take samples from outflowing product peak at appropriate times
- Wait until dispersed reagent slug has all passed the collection valve

The solution was evaporated to dryness in-vacuo, re-dissolved in EtOAc (50 ml), washed with water (50 ml) and brine (50 ml), dried (MgSO4), filtered and the filtrate evaporated to dryness in-vacuo. This gave a pale yellow gum which was further purified by column chromatography (SiO2, 25% EtOAc/Heptane) to give a colorless liquid Yield = 4.12g, 87% isolated yield.



Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
2		4.53	1e+007	95.63	0	1e+008	
3		4.67	6e+005	4.37	0	9e+006	

Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		4.41	3e+005	0.40	0	3e+006	
3		4.64	4e+007	56.86	0	2e+008	
4		4.84	2e+007	38.18	0	1e+008	
5		5.37	7e+005	1.01	0	8e+006	
6		5.43	2e+006	2.55	0	1e+007	
7		5.79	3e+005	0.39	0	2e+006	
8		5.84	3e+005	0.40	0	2e+006	
9		6.09	1e+005	0.19	0	1e+006	

Peak ID	Compound	Time	Mass Found
2		4.53	

Combine (267:273-(253:256+282:285))

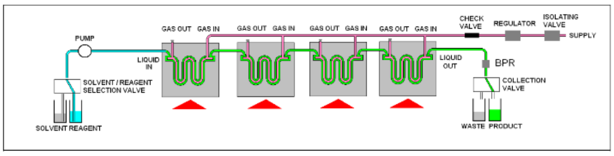
Peak ID	Compound	Time	Mass Found
3		4.64	

Combine (273:279-(256:259+291:294))

Further Scaleup

In the previous section, it was shown how 25 ml of solution A (25 mmol) were processed and collected over an experimental period of < 2 hrs as shown above. After work up and purification an isolated yield of 4.12 g was recorded, equal to a mass transfer in continuous use of 3.7 g/hr. As described earlier reactions of this type carried out in batch reactors typically take between 12-24 hrs. Extrapolating this experiment suggests a yield of 89g/24 hrs under continuous reaction conditions.

If the maximum four tube reactors are connected in series and the same reaction conditions are applied, (40 min residence time, 150 °C and 30 bar CO) a steady state mass transfer of 14.8 g/hr or 356 g/24hrs can theoretically be achieved.



Conclusion

This study demonstrates the capability of the Vapourtec R-Series system to allow difficult to scale in batch reactions to be developed and optimized to demonstrate conditions that allow safe and controlled scale up in flow. The continuous flow of this system allows the user to facilitate reactions at far higher scales than are typically carried out in pressurized batch reactors.

It has been shown that the bench top Vapourtec R-Series reactor coupled with the Vapourtec tubein- tube gas/liquid reactor opens up development scale carbonylation reactions to general laboratories.