Minimizing Isobutylene Emissions from Large Scale *tert*-Butoxycarbonyl Deprotections

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Abstract:

Isobutylene off-gas amounts liberated during the methanesulfonic acid-catalyzed deprotection of N-BOC-pyrrolidine in THF, methanol, ethanol, 2-propanol, toluene, and dichloromethane were measured using on-line gas-phase mass spectroscopy. While one full equivalent of isobutylene was released as an off-gas when THF was used as the reaction solvent, emissions were reduced by 65-95% in other solvents. In alcohol solvents, the corresponding alkyl *tert*-butyl ethers are formed as byproducts of the reaction as expected. In dichloromethane and toluene, oligomers of isobutylene can be formed under the reaction conditions. These results provided the basis for developing an effective acid/toluene scrubber for isobutylene that was successfully employed on the pilot plant scale.

Introduction

The *tert*-butoxycarbonyl (BOC) fragment is commonly used throughout organic synthesis as a protecting group for amines.^{1,2} The BOC group is typically removed under acidic conditions^{1–3} in a wide variety of solvents, and one potential organic byproduct of this process is isobutylene,^{2,4} which is a VOC subject to regulation by the EPA.⁵ Because isobutylene has a boiling point (bp) of -6.9 °C, allowing it to pass through most process condensers uncontrolled and vent to the atmosphere in the absence of suitable end-of-line devices, emissions must be dealt with accordingly before a process can be run on a manufacturing scale.

The generally accepted mechanism for BOC deprotection is shown below (Scheme 1):^{2,6} Protonation of the carbonyl oxygen of the *tert*-butyl carbamate results in degradation to initially produce the unprotected amine, carbon dioxide, and the highly reactive *tert*-butyl cation, 1,^{2a,6,7} which can decompose to isobutylene, 2,^{2,4} in the absence of suitable trapping reagents. On laboratory scale, **1** is often trapped

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with scavengers^{1,7,8} such as thiophenol^{1,7} to form an unreactive byproduct, **3a**; however, in an industrial setting, this can be prohibitive in terms of cost, worker exposure, and added purification.

In the absence of a powerful scavenger, **1** can be trapped in other manners. When trifluoroacetic acid is used, reaction with the conjugate base can form the *tert*-butyl trifluoroacetate ester, **3b**;^{6,7,8a,9} however this typically will not occur with methanesulfonic or other nonnucleophilic strong acids. It has also been noted that water and alcohols will encourage formation of *tert*-butyl alcohol^{2a,11b} or the corresponding alkyl *tert*-butyl ethers, **3c**,^{10,11} which may provide a practical approach to reducing isobutylene emissions but will be somewhat limited by potential functional group incompatibilities.

Initially, we set out to measure isobutylene emissions from BOC deprotections in different solvents with two goals. First, we wanted to identify solvents that produce high isobutylene emissions, and second, we wished to measure the isobutylene trapping efficiency of different alcohol solvents. To this end, we decided to use on-line mass spectrometry to independently measure the amounts of both carbon dioxide and isobutylene released from the reaction in real-time,¹² since

Scheme 1. Byproducts of 'BOC deprotection



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the rate of carbon dioxide production also provides a convenient measure of reaction rate and completion.

In this study, we report a method for quantifying absolute amounts of isobutylene and carbon dioxide released during BOC-deprotections in a variety of solvents using on-line gas phase mass spectrometry as the analytical method. Based on these results, a general solution for externally scrubbing isobutylene from reaction off-gas streams with greater than 99% efficiency was developed and employed successfully on the pilot plant scale.

Results and Discussion

Measurement of Isobutylene Off-Gas from Common Solvents. Using the methodology described in the Experimental Section, carbon dioxide and isobutylene off-gas results were obtained for the methanesulfonic acid (MSA) catalyzed deprotection of *N*-BOC-pyrrolidine, **4**, in several solvents (Scheme 2) using on-line gas-phase mass spectrometry.¹³ The results are summarized in Table 1.

Scheme 2. Model deprotection reaction

Table 1. Summary of off-gas results

solvent	temp (°C)	isobutylene (equiv)	CO ₂ (equiv)
THF	45	1.12	1.07
toluene	45	0.25	0.91
dichloromethane	20	0.15	0.99
methanol	20	0.10	0.97
ethanol	40	0.29	1.08
2-propanol	45	0.31	0.94

From Table 1, it is immediately apparent that isobutylene emissions are greatest when THF is used as the solvent. Emissions from methanol are the lowest (0.10 equiv, Table 1), presumably due to formations of methyl *tert*-butyl ether (MTBE).^{10,11a} Isobutylene emissions from ethanol and 2-propanol are approximately 3 times higher (0.29 equiv and 0.31 equiv, respectively, Table 1), likely because of steric effects.¹⁰ Alcohols with less steric bulk are expected to favor nucleophilic substitution over elimination, resulting in higher ratios of the corresponding alkyl *tert*-butyl ether to isobutylene.

Because these reactions were performed with a constant stream of flowing helium as a reference gas, often at elevated temperatures to increase the reaction rate (the measured amount of isobutylene was relatively unaffected by temperature), the *tert*-butyl ethers that form in alcohol solvents could not be accurately quantified by gas chromatography due to evaporative losses. Evidence for this was observed in the mass spectra, as unique signals arising from the ethers were detected (m/z = 73 for MTBE; 59 for ETBE, 'PTBE). As a result, it was often observed that the isobutylene signal (m/z = 56) would not return to baseline when the reaction was performed in alcohol solvents, since isobutylene itself is a mass fragment of the *tert*-butyl ethers. To obtain accurate, quantitative results, the overlap at m/z = 56 was corrected by using the unique signals for each ether, e.g., the relative intensities of the signals at 56 and 73 for pure MTBE were used to adjust for the signal overlap with isobutylene and correct the baseline.

One point worth mentioning is that a lag time between the carbon dioxide and isobutylene flow profiles was observed in some cases. For example, the flow and total offgas profiles for the reaction performed in THF are shown below (Figure 1). While the carbon dioxide flow profile for the reaction in THF returns to baseline in approximately 30 min, it takes several hours for the isobutylene emission to be complete. Interestingly, this effect is not observed in the case of alcohols. One possible explanation for this behavior is that isobutylene has a limited, although significant, solubility in THF. Because the reaction is performed under flowing helium, the isobutylene in the headspace is constantly being removed, which slowly drives the remaining isobutylene out of solution.



Figure 1. CO_2 and isobutylene off-gas profiles. CO_2 (dashed lines) and isobutylene (solid lines) flow and total off-gas profiles for the BOC deprotection (Scheme 2) in THF at 45 °C. The total off-gas profiles were generated by integration of the corresponding flow profiles, using the ideal gas law to obtain molar equivalents.

This effect is observed for the reactions performed in dichloromethane and toluene as well, although to a much lesser extent. When taken in conjunction with the fact that isobutylene emissions from dichloromethane and toluene were relatively low (Table 1), it became apparent that another process was also occurring. In the case of toluene, formation of at least some 4-*tert*-butyltoluene was expected;^{8a,14} however, GC analysis indicated that this accounted for at most 5% of the isobutylene. Instead, it was determined that, under the reaction conditions, the cationic polymerization of isobutylene^{11,15} to form nonvolatile oligomers was in fact responsible for the observed low emissions (Scheme 3).¹⁶

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Scheme 3. Oligomerization of isobutylene



Table 2. Laboratory scrubber results

run no.	scrubber medium	amount (g)	acid	amount (g)	isobutylene (g)	scrubber efficiency (%)
1	methanol	198	MSA	8	1.5 ^a	0
2	methanol	350	concd HCl	10	1.5^{a}	0
3	toluene	225			1.5^{a}	0
4	toluene	225	MSA	8	1.5^{a}	99.6
5	toluene	225	MSA	8	36 ^b	99.6
6	toluene/methanol	173/40	MSA	8	1.5^{a}	0

^{*a*} Based on isobutylene flow = 10 sccm over 60 min. ^{*b*} Based on isobutylene flow = 10 sccm over 24 h.

Using dichloromethane as the solvent, this was verified by using a standard workup procedure to isolate the organic soluble matter from the reaction mixture. The pyrrolidine– MSA salt was extracted with water, and the organic layer was washed with aq. NaHCO₃ to remove the remaining MSA. The organic layer was dried and concentrated, leaving a clear liquid that accounted for 97% of the isobutylene that was not evolved from the reaction. Combustion analysis and IR spectroscopy are consistent with the liquid being isobutylene oligomers (see Experimental Section).

Development of an Isobutylene Scrubbing System. As described above, appropriate choice of solvent can provide a primary method for reducing isobutylene emissions during BOC deprotections; however, it is recognized that there will be instances where solvents such as THF must be used for optimal reaction conditions. In the absence of a suitable endof-line device, the use of an external scrubber will be necessary to ensure that isobutylene emissions will meet the environmental regulatory limits. Furthermore, an efficient external scrubbing system is a generally applicable solution for all BOC deprotections, regardless of solvent.

Based on the above data, the most promising scrubbing systems appeared to be either methanol/acid to form MTBE or toluene/acid to form poly(isobutylene); dichloromethane was not considered due to its relatively low boiling point. Taking into account the limitations of the pilot plant gas scrubbing system, the laboratory studies were all performed at room temperature, yielding the following results (Table 2).

Runs 1 and 2 were performed using methanol as the solvent with methanesulfonic acid and concentrated HCl as the acid source, respectively. Under the scrubbing conditions,



Figure 2. Isobutylene scrubbing experiment with 225 g of toluene and 8 g of methanesulfonic acid (from Table 2, run 4). The isobutylene flow was set at 10 sccm and the helium flow was set at 100 sccm for this experiment. The response ratios for isobutylene/helium (56/4) at the scrubber inlet (solid line) and outlet (dashed line) are shown. Integration of the two profiles gives a scrubbing efficiency of 99.6%.

no reaction with isobutylene to form MTBE was observed in either case.

Runs 3, 4, and 5 were all performed using toluene as the solvent. Run 3 was performed as a control with no acid present to catalyze oligomerization, and there was no observable scrubbing of isobutylene as expected. Run 4 was the initial run using methanesulfonic acid (MSA), which formed a dispersion due to its low miscibility with toluene. Despite this drawback, greater than 99% isobutylene removal from the vapor stream was observed (Figure 2). In Figure 2, the response ratio for isobutylene to the argon reference gas is plotted at the scrubber inlet and the scrubber outlet,¹³ and it can be easily seen that very little isobutylene is present after the vapor stream has passed through the scrubbing medium. Weighing of the scrubber bottle after the experiment indicated that the mass of the solution had increased by approximately 1.45 g, indicating good agreement with the theoretical input.¹⁷ Run 5 was an experiment to determine the amount of isobutylene that could be taken up by the scrubber medium before efficiency was reduced, if at all. After 24 h, approximately 36 g of isobutylene were introduced into the scrubber with little or no reduction in scrubbing efficiency.¹⁸

Run 6 was an experiment to determine if methanol could be added to the toluene/MSA solution to increase miscibility.

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⁽¹⁶⁾ When the deprotection in toluene was performed at elevated temperatures (70-80 °C), unique signals in the mass spectrum corresponding to diisobutylene were detected.

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⁽¹⁸⁾ It should be mentioned that, as expected, a substantial increase in the volume of the scrubber solution was noted during the course of this experiment, which had to be terminated to avoid overflow of the solution into the gas lines.



Figure 3. Toluene/MSA scrubber efficiency vs amount of MSA. Keeping the same amount of toluene (225 g), the scrubber efficiency is shown to decrease with decreasing amounts of methanesulfonic acid. At 1.2 g of MSA, the scrubbing efficiency falls to zero.

Using what was determined to be a minimum amount of methanol, the results were disappointing as the scrubbing efficiency was completely destroyed.

Additional experiments were performed to determine the minimum concentration of MSA required to maintain good scrubbing efficiency (Figure 3). As shown in Figure 3, halving the amount of MSA from 8 g (Table 2, Run 4) to 4 g resulted in a small decrease in scrubbing efficiency from greater than 99% to around 97%. When the amount of acid was reduced to 2.0 g, the scrubbing efficiency was further eroded to 80%. Further reduction of the acid to 1.2 and 0.8 g, however, completely eliminated the scrubbing efficiency, indicating that there is likely a critical concentration in the range 1.2-1.7 g of MSA per 225 g toluene that is required for the oligomerization reaction to occur under these conditions.

Isobutylene Scrubbing on the Pilot Plant Scale. Recently, a reaction was scaled-up in the Pfizer Groton Pilot Plant facility in which two BOC groups were removed in a single step using THF as the solvent. To reduce isobutylene emissions, an external toluene/MSA scrubber using the conditions from Table 2, Run 4 was employed. The reaction was run in 3×500 gallon batches, and the scrubbing solution was not changed between runs. Before the third and final batch, the mass spectrometer was interfaced with the pilot plant scrubber train so that we could measure the effectiveness of this scrubber on scale. Using house nitrogen as the carrier and reference gas, the data in Figure 4 were collected.

Because the house nitrogen flow fluctuated throughout the course of the experiment, the data in Figure 4 is noisier than that obtained on the laboratory scale (Figure 2). This does not impact the results, however, since the flow is equal at both the scrubber inlet and outlet. From these data, we can estimate that approximately 97% scrubbing efficiency was achieved on scale for this run. While these results are not as exceptional as the >99% efficiency achieved in the laboratory, possibly due to different mixing of the MSA and toluene within the pilot plant scrubber system, the 97% reduction in isobutylene emissions is viewed as a successful



Figure 4. Mass spectrometry profiles for the pilot plant scrubber inlet (solid line) and outlet (dashed line). Isobutylene off-gas is observed at the scrubber inlet starting at 2 h when concentrated HCl is added to the reaction. At 14 h, the N_2 sweep is increased to purge the remaining gases from the reactor headspace. Integration of the profiles shows 97% scrubber efficiency.

outcome for the first attempt to employ this novel scrubber on scale.

Conclusions

By performing calibrations with isobutylene and carbon dioxide using helium as a reference gas, we have demonstrated that gas-phase mass spectrometry can be used as an on-line analytical tool to measure the rate at which these off-gases are liberated during BOC deprotections. Simple integration of the resulting flow profiles produced off-gas totals, which were used to determine the effectiveness of common organic solvents at reducing isobutylene emissions.

It was determined that in THF all of the isobutylene is liberated as a reaction off-gas, such that external scrubbing will be required if this solvent is used on a manufacturing scale. In alcohol solvents, the *tert*-butyl cation is partially trapped as the corresponding alkyl *tert*-butyl ethers. Methanol is most efficient for this purpose showing a 90% trapping efficiency, while ethanol and 2-propanol are not as efficient likely due to steric effects.¹⁰ Surprisingly, isobutylene emissions from both dichloromethane and toluene were found to be relatively low as well due to the propensity of isobutylene to polymerize under the reaction conditions to produce nonvolatile oligomers.¹⁵

One question that naturally arises is why isobutylene oligomerizes in dichloromethane and toluene but not in THF. Two reasons for this behavior are offered at this time: (1) THF is a Lewis base which will favor E1 elimination of the *tert*-butyl cation to form isobutylene and (2) the acidity of methanesulfonic acid is reduced in THF, as the solution will only be as acidic as the corresponding oxonium ion.⁹ Evidence for reason (1) is provided by the fact that both ethanol and 2-propanol exhibit higher isobutylene emissions than toluene and dichloromethane, while methanol shows the greatest trapping efficiency.¹⁰ However, the fact that in our laboratory scrubbing studies the methanol/MSA solution showed zero trapping efficiency suggests not only that reason (2) may contribute as well but also that during a BOC

deprotection reaction it is the initially released *tert*-butyl cation that reacts with methanol to form MTBE, and not one formed from direct protonation of isobutylene. This argument is further supported by the fact that, in our laboratory scrubbing studies, a toluene/MSA solution provided >99% scrubbing efficiency; however, the introduction of a minimum amount of methanol to promote miscibility reduced this to zero. Overall, these results suggest that, in THF, the equilibrium between isobutylene and the *tert*-butyl cation may not be favored enough to promote oligomerization under the reaction conditions, and since the initially formed *tert*-butyl cation (the manner that it does with alcohols, the only available route is elimination to form isobutylene which is inevitably released as an off-gas.

On the pilot plant scale, the toluene/MSA scrubber developed in the laboratory exhibited 97% efficiency for the removal of isobutylene from the reactor effluent stream. While this is successful, it is not as efficient as the >99% efficiency that was observed on the laboratory scale. It is suggested that this may be due to differences in mixing of the relatively immiscible MSA and toluene in the two different scrubbing systems and may be supported by the fact that on the laboratory scale a mere 6.5-fold reduction in the amount of MSA reduces the scrubbing efficiency to zero. In other words, if the oligomerization reaction is that sensitive to the concentration of acid, incomplete or even different degrees of dispersion may lead to the observed differences in scrubbing efficiency.

In conclusion, we have demonstrated that isobutylene emissions from BOC deprotection reactions can be heavily influenced by choice of solvent, which should be the first consideration when a reaction is being optimized for production scale. In addition, we have developed a novel scrubber that takes advantage of the fact that, under the right conditions, isobutylene reacts with itself to form nonvolatile products. In addition to being chemically efficient, this scrubbing system may also be economically efficient. Since there is no need for a stoichiometric trapping reagent, the scrubbing solution can be recycled and utilized for several batches with little reduction in isobutylene removal efficiency.

Experimental Section

Materials and Methods. *N*-BOC pyrrrolidine and methanesulfonic acid were purchased from Aldrich and used without further purification. Matheson flow controllers and a Matheson gas mixing system were used for delivery of helium, carbon dioxide, and isobutylene at constant flow rates. An Amatek Dycor ProMaxion multiport mass spectrometer was used to obtain gas-phase measurements. FT-IR spectra were collected using an MT Autochem ReactIR 4000 with a DiComp ATR probe. Microsoft Excel and Kaleidagraph for Windows were used for all of the data analysis.

Measurement of Isobutylene and Carbon Dioxide Off-Gas. The diagram in Figure 5 details the experimental setup used for our quantitative off-gas analysis. The reaction was performed in a pressure-tight HEL Automate Hastelloy vessel containing one gas inlet port, one gas outlet port, and one dosing port. A constant flow of helium was supplied as the carrier gas at the inlet. The outlet line was split, with one line going to the mass spectrometer and the other to an oil bubbler to ensure that a helium atmosphere is maintained throughout the system.



Figure 5. Reactor setup for off-gas analysis of BOC deprotections.

Calibration curves were generated using known flow ratios of isobutylene and carbon dioxide relative to the helium carrier gas (Figure 6). In Figure 6, the response ratio for the isobutylene ion peak at m/z = 56 relative to the helium ion peak are plotted as a function of the input flow ratio. The slope of the resulting linear fit provides a calibration factor that relates the ion response ratio to the flow ratio. By using the helium carrier gas with constant flow as an internal standard, the flow profiles for carbon dioxide and isobutylene can then be constructed.



Figure 6. Isobutylene response calibration plot. The response ratio for isobutylene (m/z = 56)-helium (m/z = 56) is plotted versus the gas input flow ratio (\bigcirc) with helium at a constant flow rate of 5 sccm. Linear regression (solid line, R = 0.999 27) provides the calibration factor of 2.597 in this instance.

Sample Calculation. To demonstrate the manner in which the flow profiles were obtained, the following sample calculation quantifying the carbon dioxide off-gas for the BOC deprotection run in methanol at 20 °C is presented.

First, the response ratio profile for the carbon dioxide ion peak (m/z = 44) relative to the helium ion peak (m/z = 4) is plotted. Dividing the response ratio by the calibration factor of 4.535 provides the flow ratio profile for carbon dioxide relative to helium (Figure 7).

Because the flow rate of helium is fixed at 5 sccm (sccm = standard cubic centimeters per minute), multiplying the



Figure 7. Response ratio (solid line) and flow ratio (dashed line) for carbon dioxide (44) relative to helium (4) for the reaction performed in methanol at 20 $^{\circ}$ C.

flow ratio by 5 gives us the actual carbon dioxide flow profile in sccm (Figure 8). Integration of the flow profile with respect to time gives us the total amount of carbon dioxide liberated from the reaction, which is 316 mL (1 scc = 1 mLat STP) (Figure 8).



Figure 8. Flow profile (solid line) and total (dashed line) for carbon dioxide off-gas from the reaction performed in methanol at 20 $^{\circ}$ C.

Based upon 2.5 g of starting material, the expected amount of CO_2 liberated is shown in eq 1:

2.5 g ×
$$\frac{1 \text{ mol}}{171.24 \text{ g}}$$
 × $\frac{22.4 \text{ L}}{1 \text{ mol}}$ = 0.327 L = 327 scc (1)

Therefore, the total amount of CO_2 liberated, as obtained from the mass spectroscopy data, is 316/327 = 0.97 equiv.

Deprotection of *N***-BOC**–**Pyrrolidine.** Typically, *N*-BOC– pyrrolidine (2.5 g, 2.6 mL, 14.6 mmol, 1 equiv) and 25 mL of solvent were charged to the reactor and brought to temperature. The vessel was then purged with a constant helium flow of 5 sccm until constant baseline readings for the atmosphere were obtained on the mass spectrometer. Methanesulfonic acid (7.0 g, 4.7 mL, 73.0 mmol, 5 equiv) was introduced via syringe through the dosing port, which was kept sealed with a PTFE coated silicone rubber septum seated above a stainless steel ball valve. Upon addition, vigorous carbon dioxide evolution was often observed at the oil bubbler, verified by an increase in the CO₂ signal at the mass spectrometer.

Isolation of Isobutylene Oligomers from Dichloromethane. After performing the deprotection reaction in



Figure 9. Apparatus for isobutylene scrubber experiments.

dichloromethane, the solution was worked up as follows. The reaction mixture was first extracted with water (3 × 25 mL) to remove the pyrrolidine–MSA salt. The organic layer was then washed with aq. NaHCO₃ (2 × 25 mL) to remove residual MSA, collected, and dried over Na₂SO₄. After filtration, the solution was concentrated to dryness by rotary evaporation at or below ambient temperature to minimize the loss of diisobutylene (bp = 101-102 °C), producing 0.814 g of a clear, colorless liquid (83% yield). Anal. Calcd: C, 85.63%; H, 14.37% based on isobutylene. Found: C, 85.50%; H, 14.49%; N < 0.10%. FT-IR (neat): 3076 cm⁻¹ (w, C=*C*–*H*), 3025–2760 (vs, R₃*C*–*H*), 1635 (w, *C*=*C*), 1479 and 1464 (s, R₃*C*–*H*, R₂*C*–*H*₂), 1364 (vs, R*C*–*H*₃), 892 (m, C=*C*–*H*).

Isobutylene Scrubber Studies. A 250 mL glass scrubber bottle equipped with a gas dispersion frit and magnetic stir bar were employed (Figure 9). Helium and isobutylene were introduced through the scrubber inlet tube connected to the dispersion frit. The outlet tube was connected to an oil bubbler to maintain gastight conditions. The gas flow line was split immediately before and after the scrubber bottle so that both the inlet and outlet streams could be monitored simultaneously by mass spectroscopy.

Typically, 200 mL of solvent and 8 g of methanesulfonic acid were employed in the scrubber studies with magnetic stirring. The apparatus was purged with helium at a constant flow of 15-100 sccm until steady baseline readings were achieved at the scrubber inlet and outlet. Isobutylene was introduced as a square wave with a constant flow of 10-50 sccm for approximately 30 min.

The response ratio profile for isobutylene to helium as a function of time at the scrubber inlet and outlet can be used directly to obtain scrubbing efficiency. By simply integrating the area under both profiles, the efficiency can be calculated according to eq 2.

$$Efficiency = 1 - \frac{Area_{outlet}}{Area_{inlet}}$$
(2)

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