
Environmentally Friendly Methods for Large Scale *tert*-Butoxycarbonyl (BOC) Deprotections

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Groton, CT

AIChE 2004 Spring National Meeting

April 25-29, New Orleans, LA

Pfizer Global Research and Development



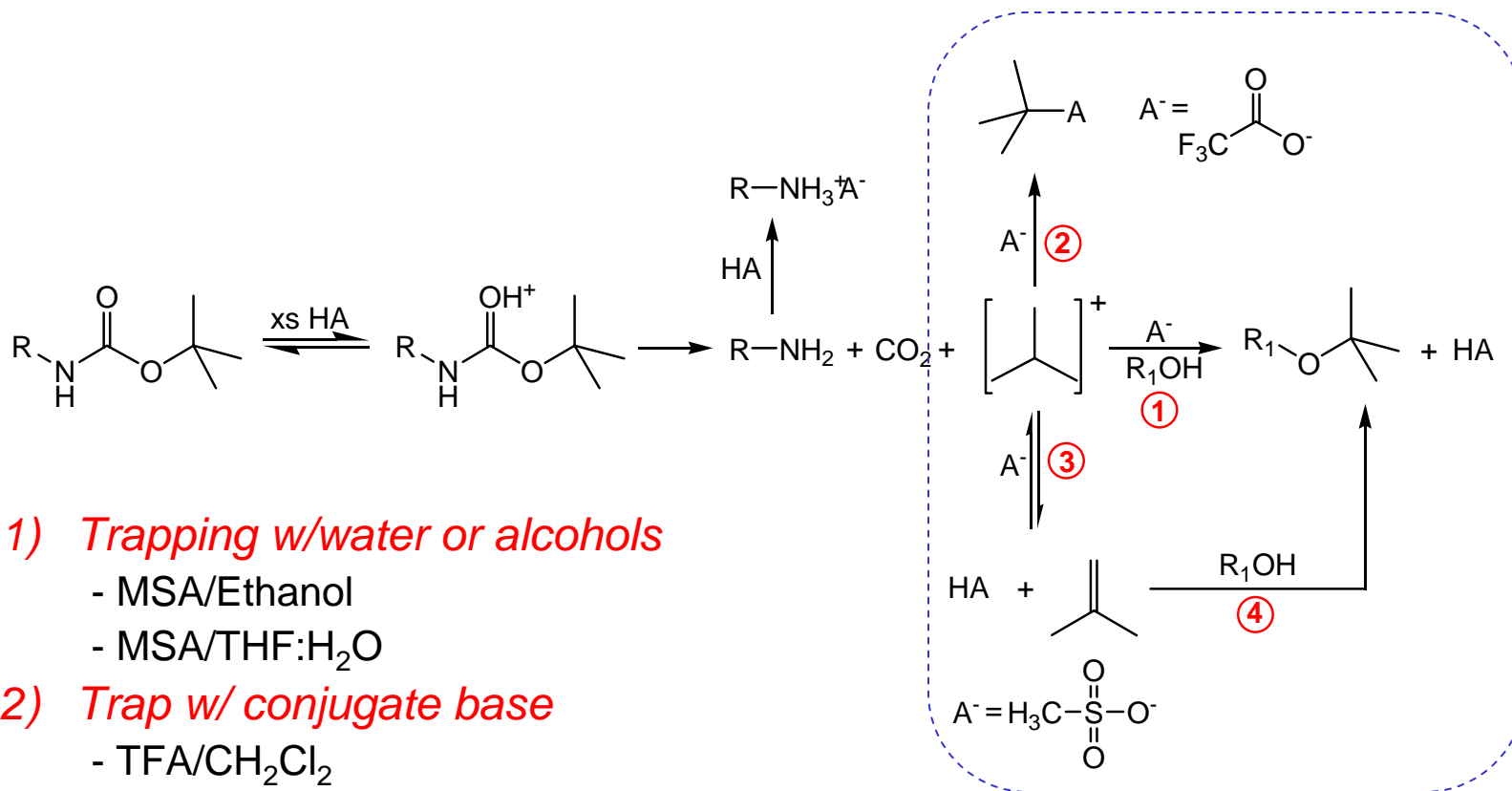
Introduction

- The *tert*-butoxycarbonyl (BOC) fragment is one of the most common protecting groups for nitrogen.
- BOC deprotection is typically effected under strongly acidic conditions, producing carbon dioxide and isobutylene as by-products.
- Isobutylene is classified as a VOC subject to regulation by the EPA, and due to its low boiling point (b.p.) of -6.9°C it can pass through process condensers uncontrolled.
- Isobutylene emissions must be dealt with accordingly before a process can be run on a manufacturing scale.

Background

- **Isobutylene emissions were a potential issue in Step 7 of a recent commercial synthesis**
 - 90:10 THF:H₂O mixture initially used as reaction solvent
 - Isobutylene emissions could exceed the environmental permit level based on the projected scale
 - Increasing water content to 70:30 THF:H₂O lowered isobutylene emissions by 3X to acceptable levels due to formation of *tert*-butanol
- **Investigation of Compound 1 Step 2**
 - Low isobutylene emissions observed using TFA/CH₂Cl₂, due to trapping as *tert*-butyl ester of TFA
 - Low emissions observed using MSA/CH₂Cl₂, presumably due to solubility of isobutylene under reaction conditions
 - In ethanol, formation of ethyl *tert*-butyl ether (ETBE) reduces isobutylene off-gas.

Potential Fates of the ^tBu Group



1) *Trapping w/water or alcohols*

- MSA/Ethanol
- MSA/THF:H₂O

2) *Trap w/ conjugate base*

- TFA/CH₂Cl₂

3) *Deprotonation to form isobutylene*

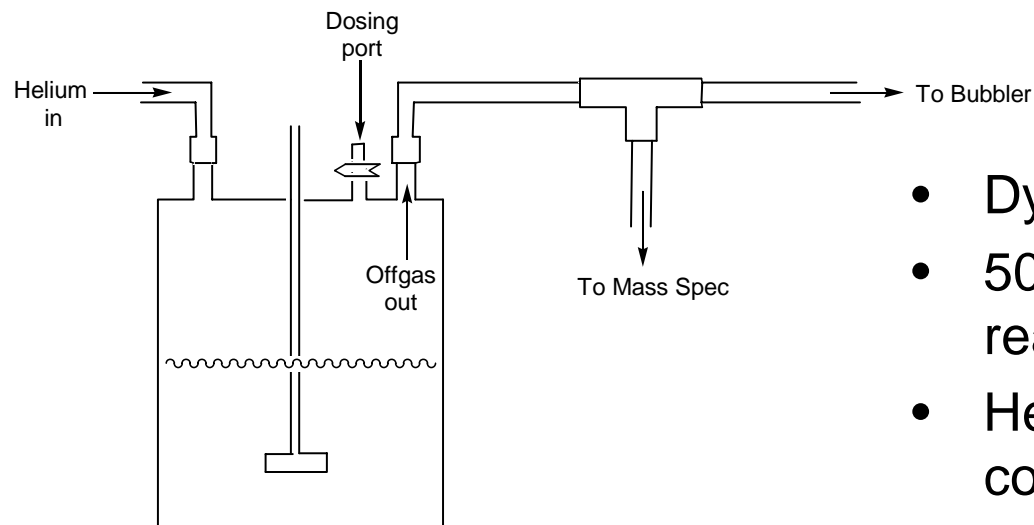
- MSA/CH₂Cl₂*

4) *Internal/external scrubbing of isobutylene*

Objectives

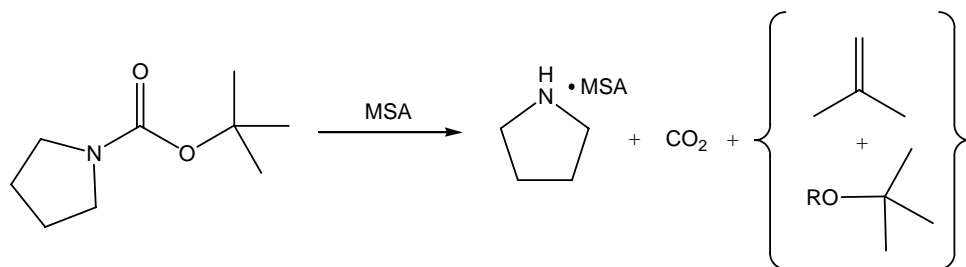
- Quantitate isobutylene emissions from common organic solvents
- Quantitate efficiency of alcohols as trapping agents
- Quantitate amount of isobutylene remaining in solution
- **Formulate strategies for controlling isobutylene emissions on scale**

Quantitation of Off-Gases by Mass Spectrometry



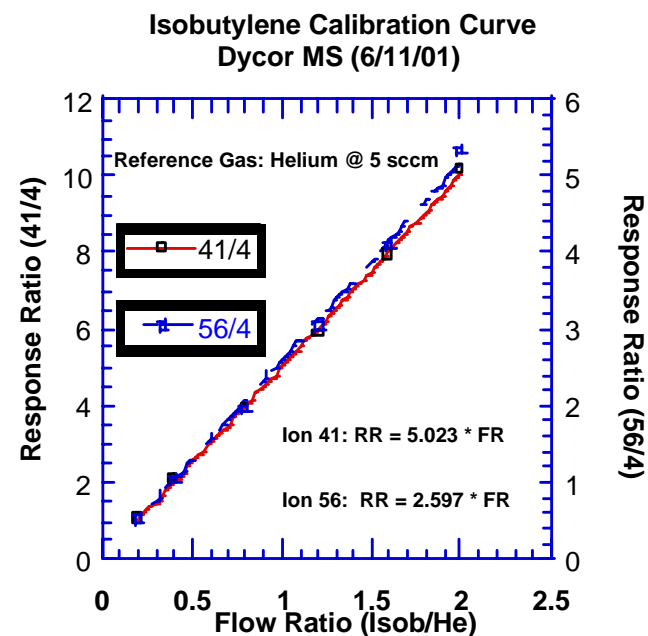
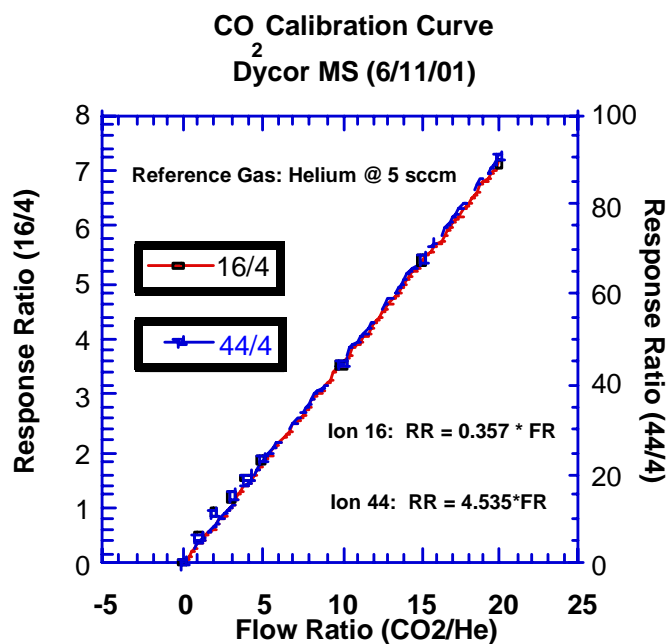
- Dycor “portable” mass spec.
- 50 ml Hastelloy pressure reactor (HEL Automate)
- Helium carrier gas used with constant flow

Model Reaction: N-BOC Pyrrolidine



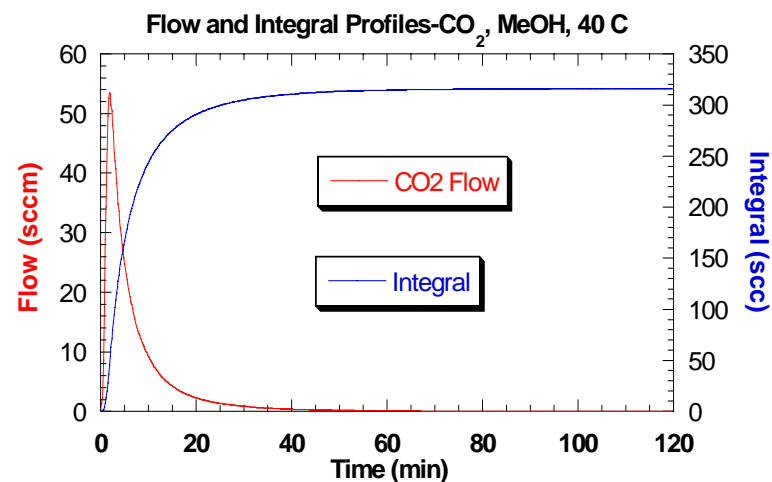
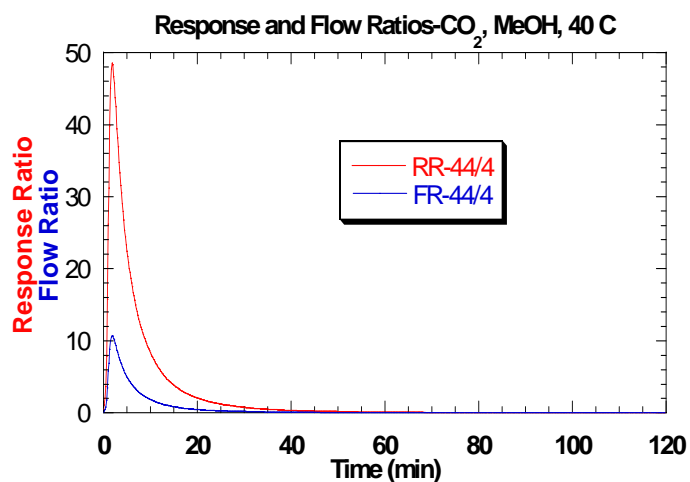
2.5 g of substrate and 10 volumes of solvent were charged to the reactor and brought to temperature. The vessel was purged with helium until constant baseline readings were obtained on the mass spectrometer. Five equivalents of MSA were introduced *via* syringe through the dosing port, and the reaction proceeded until completion.

Calibration of Mass Spectrometer



- Mass spec must be calibrated for each ion to get good quantitative results
- Helium carrier gas acts as internal standard
- Response ratios between peaks of interest and helium are obtained as a function of relative gas flow
 - Gas flow rates are adjusted and controlled using Matheson flow controllers

Extracting Flow Profiles from Mass Spectrometry Data

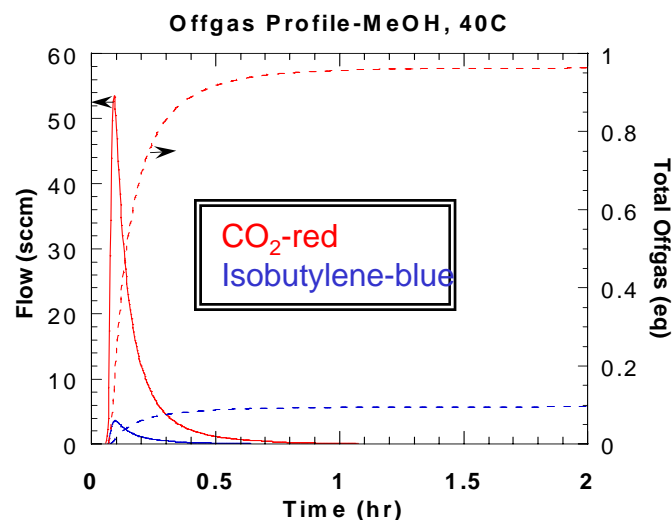
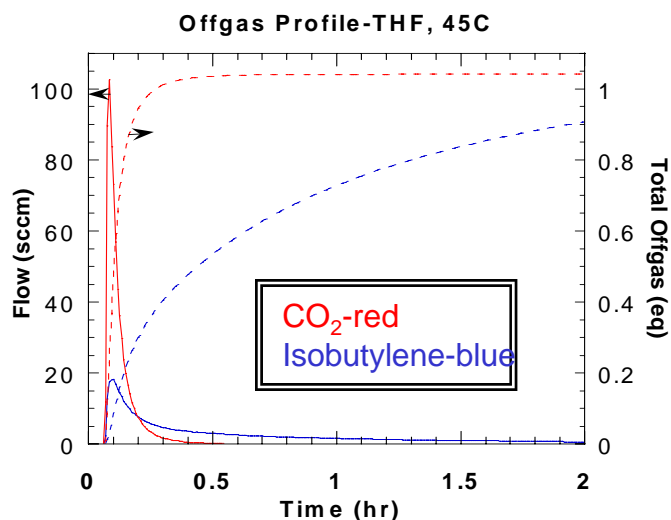


- Response Ratio (CO₂/He) is obtained from raw mass spec data and converted to a Flow Ratio (left plot) using calibration curves
- Helium is used as a carrier gas at a constant flow of 5 sccm
- Flow profile for CO₂ can be calculated as a function of time (right plot)

For 2.5 g of substrate, the expected amount of carbon dioxide is:

$$2.5 \text{ g} \times \frac{1 \text{ mole}}{171.24 \text{ g}} \times \frac{22.4 \text{ L}}{1 \text{ mole}} = 0.327 \text{ L} = 327 \text{ scc}$$

Example: Flow Profiles for MeOH, THF



- *In THF*, Isobutylene emissions are almost quantitative
 - Isobutylene comes off slower than carbon dioxide, possibly due to solubility?
- *In MeOH*, Isobutylene emissions are substantially reduced
 - Methyl *tert*-butyl ether (MTBE) formation confirmed by both mass spec and GC analysis
 - Isobutylene comes off at a rate similar to carbon dioxide

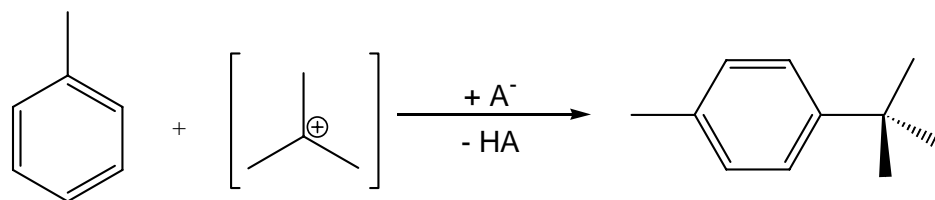
Summary of Off-gas Results for Common Organic Solvents

Solvent	Temp (°C)	Isobutylene (eq.)	CO ₂ (eq.)
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
Isopropanol	45	0.31	0.94

- Isobutylene emissions are **highest** for THF, **lowest** for Methanol
- Ethanol and Isopropanol show higher emissions than methanol
 - Likely due to steric effects upon rate of ^tbutyl ether formation
- Toluene and Dichloromethane show only modest isobutylene emissions
 - Initially believed to be due to solubility of isobutylene

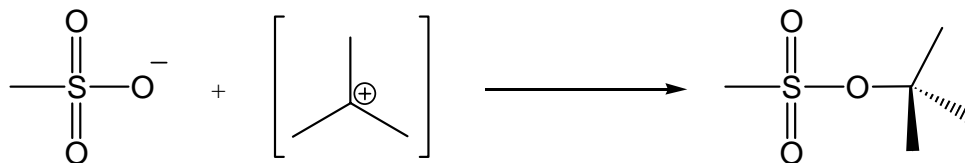
Mass Balance for CH₂Cl₂ and Toluene

- Does Isobutylene remain dissolved in solution?
 - *GC analysis gives ≤ 0.03 eq. isobutylene in solution*
- In toluene, is *tert*-butyl toluene formed?



– *GC analysis shows 0.05 eq. in solution*

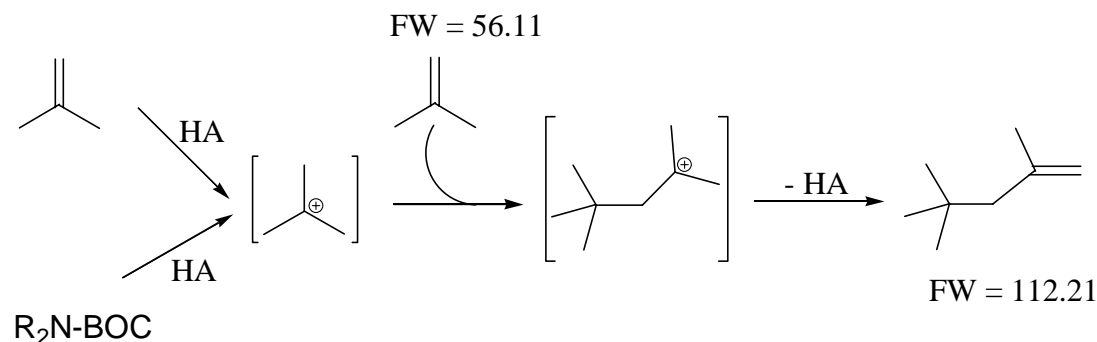
- Can the ^tBu cation be trapped as the MSA ester?



– *Addition of NEt₃ produces no additional isobutylene*

Mass Balance for CH₂Cl₂ and Toluene

- Only one remaining possibility... *oligomerization!*



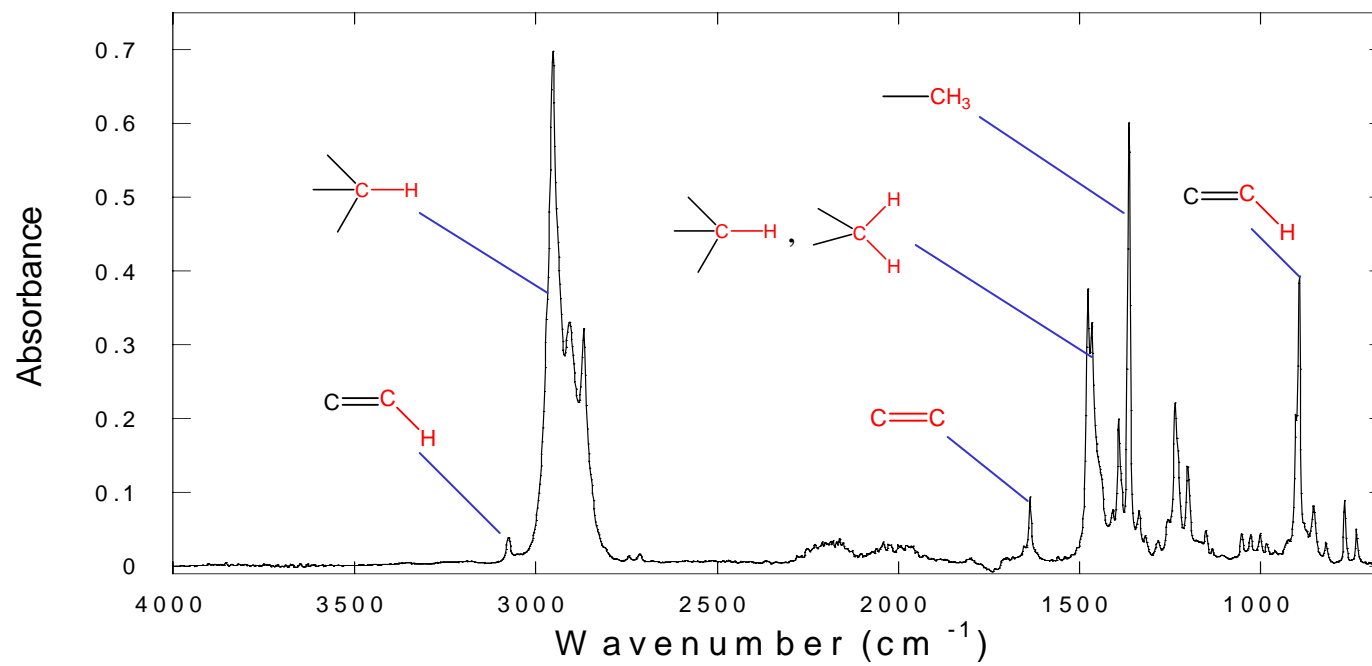
- Mass ions for diisobutylene are observed during deBOC in toluene at elevated temperatures
- GC analysis shows approx. 0.03 eq. diisobutylene in toluene, 0.10 eq. in dichloromethane
- *“Missing” mass must be due to non-volatile higher oligomers*

Isolation of Isobutylene Oligomers

- Reaction performed in dichloromethane with 3 g (17.5 mmol) of substrate, followed by standard organic workup
 - Extract pyrrolidine•MSA with water
 - Wash organic layer with aq. NaHCO_3 , dry over Na_2SO_4
 - Filter, concentrate at room temp to minimize loss of diisobutylene
 - 0.814 g of clear, colorless liquid isolated
- Based on mass of isobutylene, this translates to 14.5 mmol of product
 - 83% *yield* based on starting material
 - 97% *yield* based on missing mass

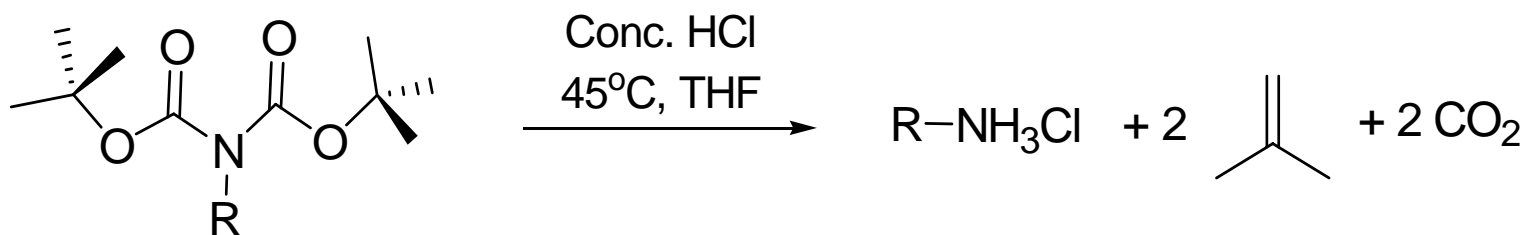
Characterization of Isobutylene Oligomers

- **Combustion analysis:**
 - Calc. 85.63% C, 14.37% H based on isobutylene
 - Found 85.50% C, 14.49% H, <0.10% N
- **IR spectrum of neat material**



BOC Deprotection of Compound 2

- Step 3 of Compound 3 synthesis involves removal of two BOC groups in THF.
- Process set to be scaled up in Groton Pilot Plant in three batches in May 2003.



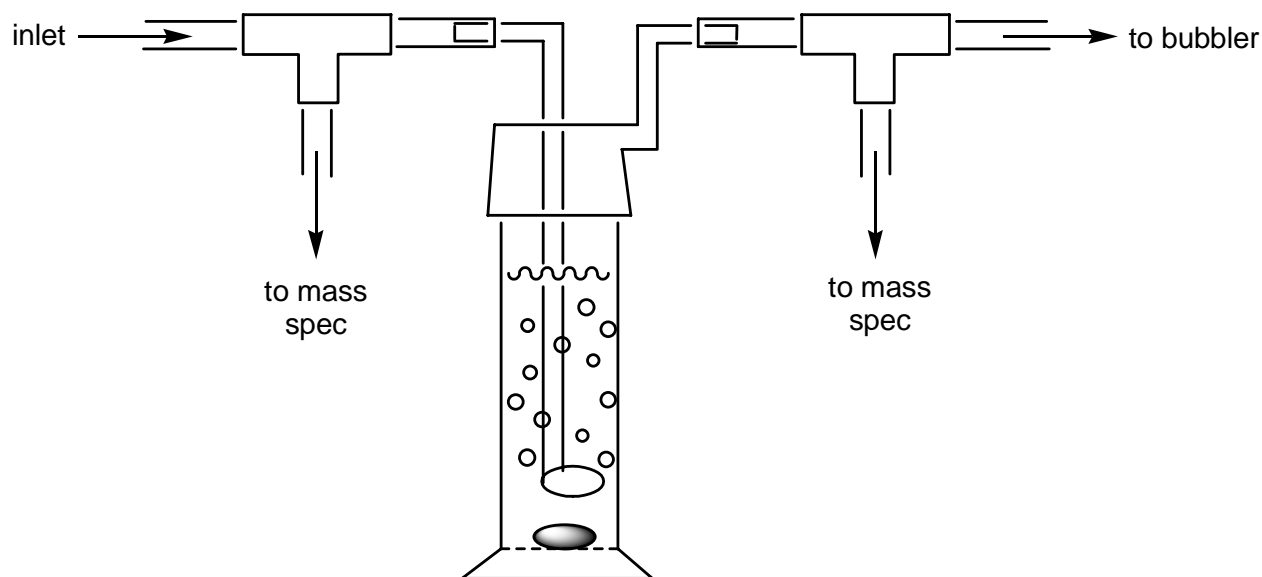
- Use of THF as the reaction solvent necessitates external scrubbing of isobutylene.

Isobutylene Scrubbing Strategies

- Use acid/MeOH to form MTBE
 - *Advantage:* Readily available materials, esp. if HCl can be used.
 - *Disadvantage:* Relatively low boiling solvent, disposal of MTBE
- Use acid/Toluene to form isobutylene oligomers
 - *Advantage:* High boiling solvent, oligomers are simple, low-reactive hydrocarbons
 - *Disadvantage:* Not as common as methanol, most acids are immiscible with solvent
- Use aq. KMnO_4 to oxidize isobutylene
 - *Advantage:* Precedence in PGM
 - *Disadvantage:* Cost and cleanup

Experimental Setup

- Use argon as carrier gas and internal standard
 - Introduce isobutylene/argon mixture into scrubber
- Interface Dycor Multiport Mass Spectrometer at scrubber inlet and scrubber outlet
 - *No calibration is necessary to get quantitative results.*



Summary of Scrubbing Results

Table 2. Laboratory Scrubber Results

Run #	Scrubber Medium	Amount (g)	Acid	Amount (g)	Isobutylene (g)	Scrubber Efficiency (%)
1	Methanol	198	MSA	8	1.5 ^b	0
2	Methanol	350	Conc. HCl	10	1.5 ^b	0
3	Potassium Permanganate	500 ^a	-	-	0.82 ^c	66
4	Toluene	225	-	-	1.5 ^b	0
5	Toluene	225	MSA	8	1.5 ^b	99.9
6	Toluene	225	MSA	8	36 ^d	99.6
7	Toluene/MeOH	40/173	MSA	8	1.5 ^b	0

^a 5g Potassium Permanganate in 500 ml tap water.

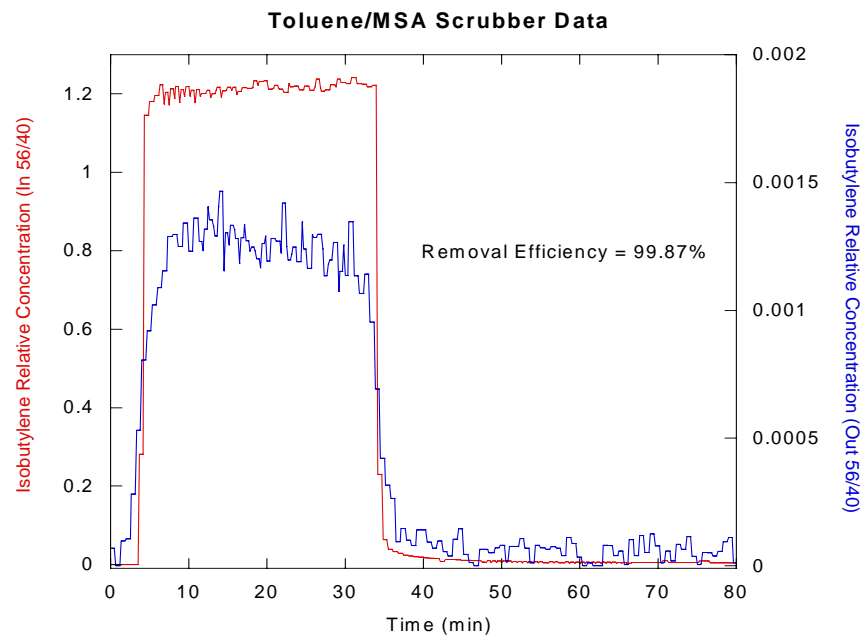
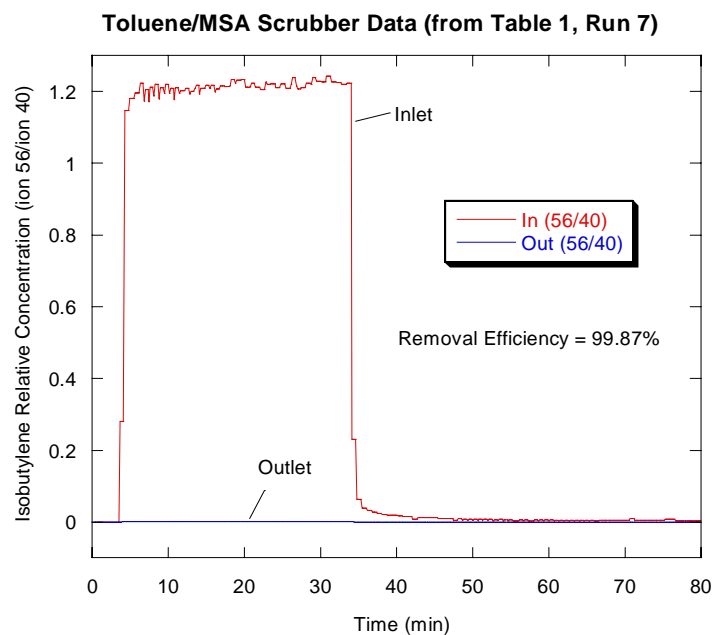
^b Based on isobutylene flow = 10 sccm over 60 minutes.

^c Theoretical amount based on 2.5 g addition of pyrrolidine (substrate, MW=171.24).

^d Based on isobutylene flow rate of 10 sccm over 24 hours.

- Toluene/MSA scrubber shows >99% efficiency in laboratory scale experiments.

Toluene/MSA Scrubbing Results



Conditions:

300 ml Toluene

10 g MSA

Argon flow rate = 10 sccm

Isobutylene flow rate = 50 sccm

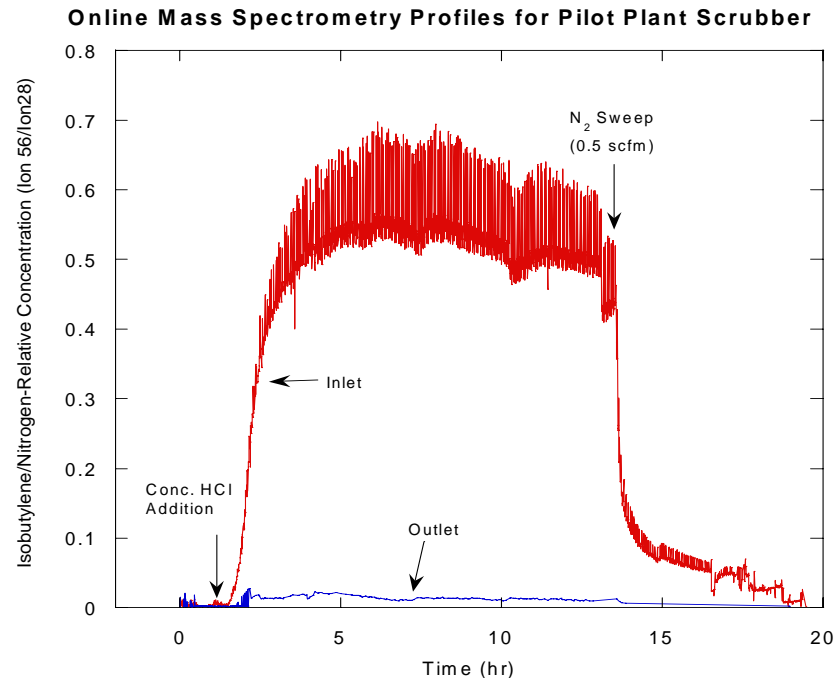
> 99% Scrubbing Efficiency

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Pilot Plant Results

- Mass spec data was acquired for Run 3 of 3 in the Pilot Plant



- Based on this data, approximately 97% scrubbing efficiency was achieved on scale.

Summary

- Isobutylene emissions are near quantitative for THF
 - Emissions decrease in the order:
THF >> *i*PrOH > EtOH > Toluene > CH₂Cl₂ > MeOH
- Methanol shows 90% efficiency for reduction of isobutylene off-gas (due to MTBE formation)
 - Efficiencies of Ethanol and Isopropanol are only around 70%, likely due to steric considerations
- Emissions are relatively low in CH₂Cl₂ and Toluene due to oligomerization of isobutylene under the acidic reaction conditions
- Using a Toluene/MSA scrubber, app. 97% isobutylene removal efficiency was achieved on scale

Acknowledgments

Steve Colgan

Angela Cady

Matt Jorgensen

Narasimhan Kasthurikrishnan