Organic Process
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Mechanistic Insights and Safety Evaluation of the Ritter Reaction Utilizing *tert*-Butyl Acetate as the *tert*-Butyl Cation Source

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Supporting Information

ABSTRACT: The Ritter reaction utilizing *tert*-butyl acetate as the *tert*-butyl cation source was investigated by in situ FTIR and calorimetry under various reaction conditions. It was established that, when a batch mode reaction in acetic acid was performed, minimal isobutylene was evolved into the headspace, thereby avoiding pressurization of the reaction vessel. The safety of these conditions is due to the equilibrium of isobutylene and acetic acid with *tert*-butyl acetate. In addition, the observation of acetic anhydride provided insight into the role of acetic acid in the mechanistic pathway.

INTRODUCTION

The Ritter reaction provides a powerful method to construct *N*-*tert*-butyl amides from nitriles. A variety of *tert*-butyl cation sources have been employed in this transformation, including *tert*-butanol,[1] isobutylene,[2] *tert*-butyl acetate,[3] and *tert*-butyl ethers.[4−6] Regardless of the *tert*-butyl cation source, isobutylene gas is considered a likely intermediate. Isobutylene is a VOC flammability class 4 gas,[7] and uncontrolled emission events have been reported in batch processing mode.[8] In 2009, our group reported Ritter reaction conditions utilizing sulfuric acid, *tert*-butyl acetate, and glacial acetic acid as solvent, whereby the acetic acid acts as a trap for isobutylene (Figure 1).[9] The reported conditions were safely and successfully scaled to a multikilogram batch process following a thorough hazard analysis.

Recently, Wirth and co-workers reported the development of a Ritter reaction as a continuous process, citing concerns about the safety of the Ritter reaction in batch mode.[10] This claim prompted us to disclose the details of the safety study conducted on our process prior to scale-up, examining both the safety profile and isobutylene emission in batch mode.

RESULTS AND DISCUSSION

Our primary focus was to develop a robust and scalable Ritter reaction. During our initial optimization, a number of conditions were identified that could perform the desired transformation. This report focuses on the hazard evaluation of three main conditions which were considered: (**Conditions A**) *tert*-butyl acetate (neat), and sulfuric acid;[3a] (**Conditions B**) *tert*-butyl acetate, toluene as solvent, and methanesulfonic acid (MSA); and (**Conditions C**) *tert*-butyl acetate, acetic acid as solvent, and MSA.[11] It was determined that reagent addition rates and initial solvent composition played an important role in the control of isobutylene emissions.

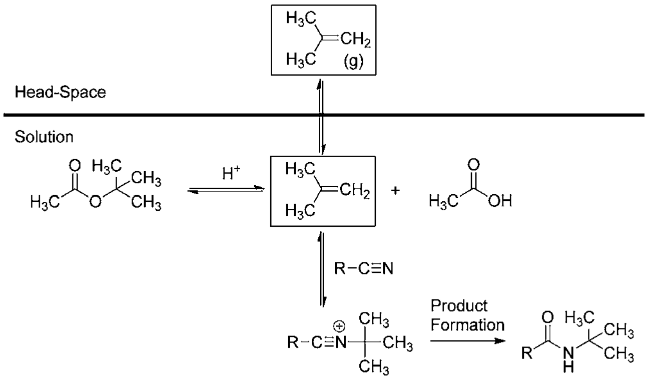


Figure 1. Proposed isobutylene/acetic acid/*tert*-butyl acetate equilibrium.

The reactions described employed 4-methoxybenzonitrile as a model substrate, and were conducted in a closed system/Mettler-Toledo RC1e calorimeter and monitored using a Mettler-Toledo ReactIR 4000 equipped with a DiComp fiber-optic probe.[12] Individual reference spectra were acquired and used to identify species within the crude reaction mixture. Trends were generated by integrating indicative IR peaks that were selected by overlaying reference spectra with those of the reaction mixture.[13] Due to the functional complexity and infrared superposition of several reaction species, isobutylene concentration could not be determined in any of the attempted experiments. ^1H NMR spectra of the crude reaction mixture were taken at the end of every experiment to confirm IR results. In all experiments, full conversion to the desired *N*-(*tert*-butyl)-4-methoxybenzamide was observed after ageing overnight, with no impact on conversion observed between conditions.

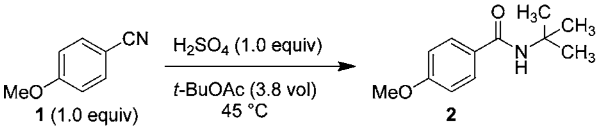
Conditions A. The conditions using sulfuric acid and *tert*-butyl acetate as solvent were performed by the addition of neat sulfuric acid over a 30 min period to a solution of 4-methoxybenzonitrile in *tert*-butyl acetate at 45 °C (eq 1).

After the acid addition was complete, the reaction was monitored over a period of 22 h. At the end of the acid

Special Issue: Safety of Chemical Processes 12

Received: January 4, 2012
Published: April 30, 2012

dx.doi.org/10.1021/op3000042 | *Org. Process Res. Dev.* 2012, 16, 2058−2063



(1)

addition, the reaction had produced 22 L/kg of isobutylene (3.5% of the total isobutylene available based upon full degradation of *tert*-butyl acetate, 13–22 psi; Table 1).[14] Controlled venting of the reaction mixture at 45 °C resulted in a minor visible release of gas into the headspace, with no change in reaction volume.

It should be noted that a 72 °C predicted adiabatic temperature rise (PATR) was calculated during the 30 min acid addition ($\Delta H_{\text{rxn}} = -103.0$ kJ/mol; Table 2).[15] The heat of reaction is believed to include a combination of: (a) the intrinsic heat of reaction, (b) heat of acid mixing, (c) heat of dosing,[16] (d) the heat of *tert*-butyl acetate decomposition into isobutylene and acetic acid, and (e) heat loss from off-gas/evaporation of isobutylene into the headspace.

During the course of the reaction, a decrease in *tert*-butyl acetate concentration and an increase in acetic acid concentration was observed by in situ IR. *N*-(*tert*-butyl)-4-methoxybenzamide increased in concentration throughout the acid addition, and reached a "steady-state" concentration at the end of addition. Accelerating rate calorimetry (ARC) analysis of these conditions revealed three exotherms: (i) 30–80 °C (due to heat of reaction), (ii) 90–100 °C, and (iii) 145–150 °C (Figure 2).[17] After quickly increasing to 3.2 bar, the pressure decreased during the initial exotherm, possibly due to isobutylene equilibration back into solution as *tert*-butyl acetate. ^{1}H NMR analysis of the bomb contents after the first exotherm showed desired product, the second exotherm showed 4-methoxybenzamide present with partial decomposition, and the third exotherm was not investigated as it was far removed from the process temperature.

Next, we examined a faster sulfuric acid addition rate at lower reaction temperature (20 °C, <1 min), followed by heating to 45 °C. The acid was manually added in one portion, and the reactor was immediately sealed. Consequently, pressure due to compression was not captured. Visible gas generation was immediately evident, and 10 psi pressure was generated after the acid addition, equilibrating to 7 psi. After thermal equilibration at 20 °C, the reactor was heated to 45 °C, and a pressure increase to 21 psi was observed which equilibrated to 15 psi after 22 h ($\Delta H_{\text{rxn}} = -63.0$ kJ/mol, 47 °C PATR; Table 2). Also noteworthy was a steep decrease in *tert*-butyl acetate observed by in situ IR immediately following the acid charge. Interestingly, the *tert*-butyl acetate concentration subsequently increased upon equilibration at 20 °C, presumably due to the sequestering action of acetic acid by reacting with isobutylene to form *tert*-butyl acetate in solution. When the temperature was raised to 45 °C, a small decrease in *tert*-butyl acetate was observed, most probably due to the isobutylene gas being driven into the headspace.[18] In conclusion, a higher overall operating pressure and evolution of isobutylene gas was observed for these conditions.

Table 2. Calorimetry data from various Ritter reaction conditions

conditions	solvent	acid	addition time	PATR[a] (°C)	heat of reaction (kJ/mol)
A	*tert*-BuOAc	H_2SO_4	30 min	72	−103.0
A	*tert*-BuOAc	H_2SO_4	<1 min	47	−63.0
B	toluene	MSA	4 h	18	−24.4
C	acetic acid	MSA	40 min	53	−56.2
C	acetic acid	MSA	<1 min	47	−67.8
C[b]	acetic acid	MSA	30 min	37	−48.9

[a] RC-1 used to calculate ATR from the measured heat of reaction; not the true adiabatic temperature rise. Thus, "predicted adiabatic temperature rise" (PATR) is reported. [b] Conditions: 2.0 equiv *t*-BuOAc; 3.0 equiv MSA, 2.0 vol acetic acid; 20 °C (no nitrile present).

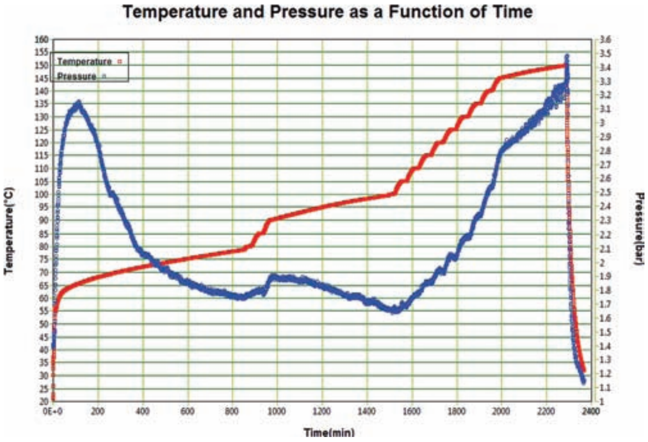


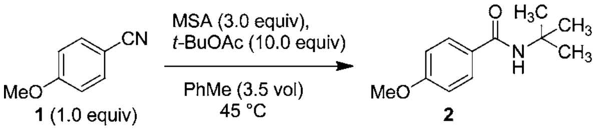
Figure 2. ARC analysis (red = temperature, blue = pressure). Conditions: 1.0 equiv of 4-methoxybenzonitrile, 1.0 equiv of sulfuric acid, 3.8 vol of *tert*-butyl acetate; components were added together at ambient temperature and heated in the ARC.

Conditions B. In 2005, conditions minimizing isobutylene emissions were reported by Diaz and co-workers for the *tert*-butoxycarbonyl (Boc) deprotection of amines on pilot-plant scale.[19] Their protocol involved polymerization of isobutylene by employing MSA/toluene as an external/internal scrubbing system. The second set of reaction conditions studied employed toluene as solvent and was performed by adding neat *tert*-butyl acetate over 3 h into a solution of 4-methoxybenzonitrile, MSA, and toluene at 45 °C (eq 2). It was postulated that the MSA/toluene conditions may create an "internal" isobutylene scrubbing system similar to that reported by Diaz and co-workers.

Table 1. Initial, compression, and steady-state pressures produced from various Ritter reaction conditions

conditions	solvent	addition time	compression pressure (psi)	initial pressure (psi)[a]	steady-state pressure (psi)[a]	isobutylene gas evolution (L/kg)[b]	% of total isobutylene available[c]
A	*t*-BuOAc	30 min	0.2	22	13	**22**	**3.5**
B	toluene	4 h	17	13	15	**17**	**1.0**
C	acetic acid	40 min	9	3	1	**1**	**0.3**

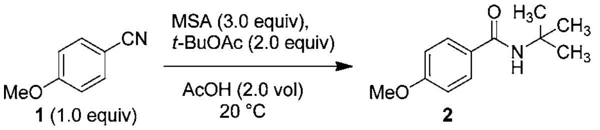
[a] Pressure corrected for compression (observed pressure − compression pressure). [b] Liter of isobutylene$_{(g)}$ per kg of 4-methoxybenzonitrile starting material. [c] Based upon the full degradation of *t*-BuOAc.



(2)

The addition of *tert*-butyl acetate produced 17 L/kg isobutylene (1.0% of the total available isobutylene, 13−15 psi; Table 1). After the reaction aged overnight, the reactor was slowly vented at 45 °C, and a vigorous off-gassing event ensued. The reactor was resealed and cooled to 20 °C. At ambient temperature, the reactor was slowly vented and did not produce any visible off-gassing. However, upon reheating the reactor to 45 °C, 9 L/kg isobutylene (0.5% of the total available isobutylene, 8 psi) was generated, and an additional off-gassing event was observed upon controlled venting. The total volume loss from venting was approximately 10%. Consequently, the bulk polymerization and internal scrubbing of isobutylene appears disrupted and not operational under these reaction conditions. The PATR was the lowest investigated (18 °C, $\Delta H_{\mathrm{rxn}} = -24.4$ kJ/mol, Table 2).[20] In situ IR analysis displayed an increase in *tert*-butyl acetate concentration as the addition progressed and then declined in concentration after the addition ceased and ageing continued, presumably due to equilibration of the system. In conclusion, these conditions produced higher operating pressure, and visible off-gassing of isobutylene was observed while venting at 45 °C.

Conditions C. The third set of conditions using acetic acid as solvent were performed by adding MSA diluted in acetic acid over 30 min to a reactor containing a slurry of 4-methoxybenzonitrile, *tert*-butyl acetate, and acetic acid at an internal temperature of 20 °C (eq 3 and Figure 3).



(3)

Minimal isobutylene was produced for the process (1 L/kg, 0.3% of the total available isobutylene, 1−3 psi; Table 1). The effect of temperature on the isobutylene buffering capacity of acetic acid was investigated by heating the crude reaction mixture. Heating the crude reaction mixture from 20 to 45 °C did not produce any additional pressure, and controlled venting of the reactor did not produce noticeable off-gassing or changes in the IR. Upon further heating from 45 to 55 °C, the pressure did not increase, and no visible off-gassing or changes in the IR were observed. A 53 °C PATR was observed for the process ($\Delta H_{\mathrm{rxn}} = -56.2$ kJ/mol; Table 2). Thermal conversion of 65% was observed at the end of the addition (35% accumulation, Figure 4). Thermal conversion was lower than the IR conversion (IR conversion at end of addition = 85%), and the difference can be rationalized by the cumulative nature of factors controlling the heat of reaction described previously. Interestingly, faster MSA addition times at 20 °C (<1 min) did not affect the pressure (≤2 psi during the entire process, $\Delta H_{\mathrm{rxn}} = -67.8$ kJ/mol, 47 °C PATR; Table 2). In an attempt to determine the heat of reaction contribution from mixing MSA with acetic acid and *tert*-butyl acetate decomposition into acetic acid and isobutylene gas, the procedure was repeated by adding a premixed solution of MSA/acetic acid into a solution of *tert*-butyl acetate/acetic acid at 20 °C (30 min addition time, nitrile omitted). Minimal pressure was produced upon addition (1 psi), and the heat of reaction was equal to −48.9 kJ/mol (Table 2). Compared to the heat of reaction observed for the Ritter reaction using these conditions, the heat associated with MSA/acetic acid mixing and *tert*-butyl acetate decomposition represents a significant factor in the total heat of reaction.

ARC analysis identified three exotherms: (i) 30−55 °C (due to heat of reaction), (ii) 75−79 °C (due to loss of the *tert*-butyl group), and (iii) 135−150 °C (not investigated, far removed from the process temperature; Figure 5).[22] It should be noted that the exotherm due to the heat of reaction under acetic acid conditions was approximately half of the exotherm observed when employing the *tert*-butyl acetate conditions (Figure 2 vs Figure 5). Furthermore, no pressure increase was observed for the system until the boiling point of AcOH had been reached, which differed from the *tert*-butyl acetate conditions as well. Overall, it was considered that the decrease in pressure during the reaction provided additional evidence of the improved safety of the acetic acid conditions.

While performing the reactions in a sealed vessel was used to understand the isobutylene equilibrium of the system, utilizing a sealed vessel on large scale was not considered practical. Conditions C were investigated under a low flow of nitrogen gas to determine any possible changes in the safety profile and/or calorimetry. For this experiment, the heat of reaction was −57 kJ/mol, and the PATR was 49 °C. Thus, no change in calorimetry (or visible generation of gas) was observed as compared to the sealed experiments. Furthermore, multikilogram manufacturing utilizing conditions C and a nitrogen sweep of the reactor headspace produced excellent results.[23]

An overall summary of the safety attributes (closed system) for the conditions investigated is listed below:

1. Conditions A involved the addition of sulfuric acid to *tert*-butyl acetate (solvent). These conditions showed the highest PATR and the highest evolution of isobutylene.
2. Conditions B involved the addition of *tert*-butyl acetate to a solution MSA and toluene. These conditions showed the lowest PATR; conversely, opening of the sealed vessel led to a visible off-gas event.
3. Conditions C involved the addition of an MSA/acetic acid mixture to a *tert*-butyl acetate/acetic acid mixture. These conditions showed the second-highest PATR observed and provided the lowest evolution of isobutylene gas. Off-gas events were not observed, even while stressing the conditions at a higher temperature.

■ MECHANISTIC INSIGHT

Our use of the Ritter reaction for API manufacturing included a crystallization of the desired *tert*-butyl amide directly out of the crude reaction mixture. On the basis of the literature, two different mechanisms have been proposed, involving two distinct intermediates whose proposed existence was not fully understood. The generally accepted mechanism for the Ritter reaction involving isobutylene in the presence of sulfuric acid is the activation of nitrile **3** by the *tert*-butyl group **4** to generate the corresponding nitrilium ion **5**, followed by formation of iminosulfate **6** (Scheme 1). Hydrolysis of iminosulfate **6** generates amide **7**.[2]

In 1966, Glikmans, Torck, Hellin, and Coussemant proposed an alternative mechanism utilizing the original Ritter reaction conditions (sulfuric acid, acetic acid as solvent).[24] This mechanism (Scheme 2) differed from the Ritter mechanism by invoking the participation of acetic acid. On the basis of the

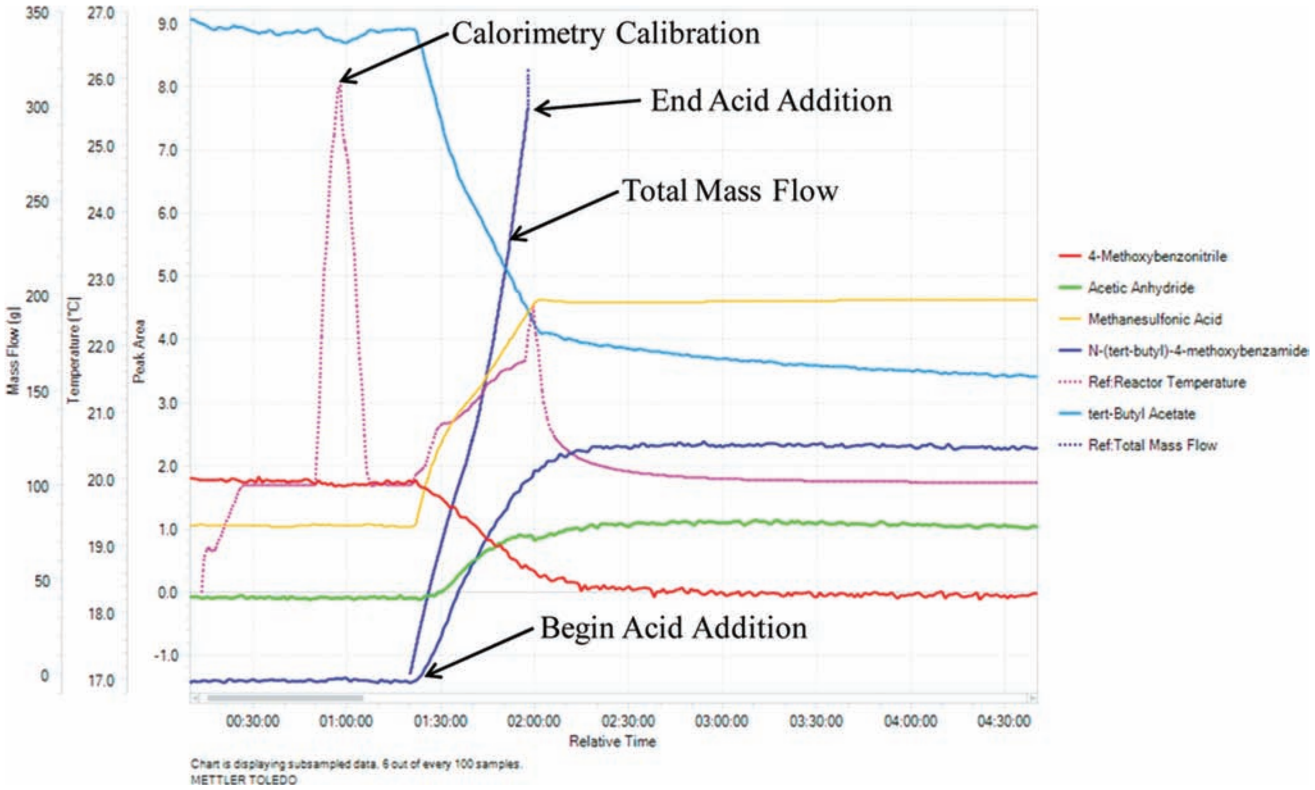


Figure 3. IR and calorimetry profiles (relative time axis cropped). Conditions C: 1.0 equiv of 4-methoxybenzonitrile, 2.0 equiv of *tert*-butyl acetate (1 vol acetic acid); 3.0 equiv of MSA (1.0 vol acetic acid); 20 °C, 30 min addition time.

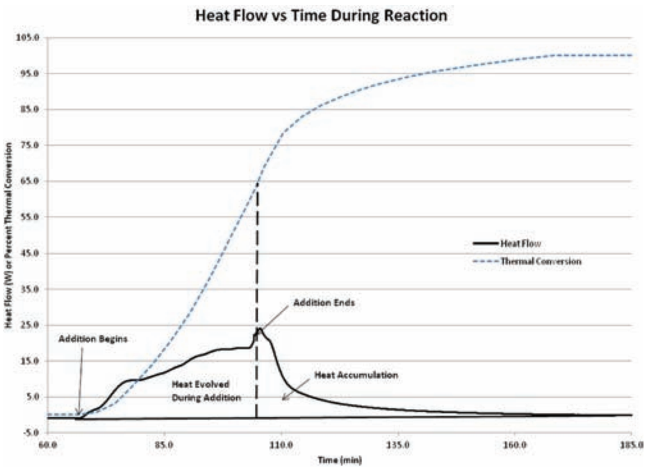


Figure 4. Heat flow vs time (time axis cropped). Conditions C: 1.0 equiv of 4-methoxybenzonitrile, 2.0 equiv of *tert*-butyl acetate (1 vol acetic acid); 3.0 equiv of MSA (1.0 vol acetic acid); 20 °C, 30 min addition time.[21]

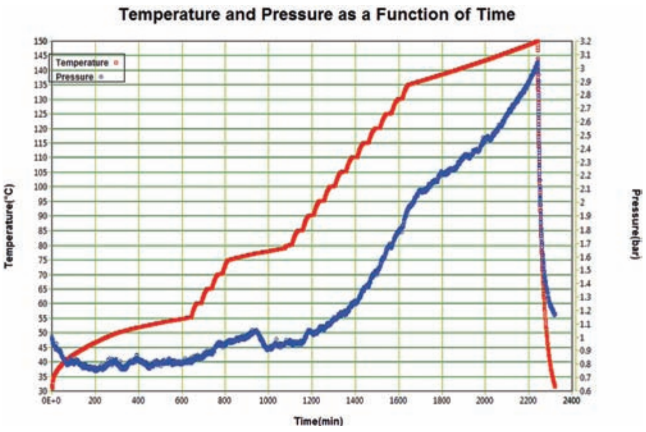


Figure 5. ARC analysis (temperature = red, pressure = blue). Conditions: 1.0 equiv of 4-methoxybenzonitrile, 2.0 equiv of *tert*-butyl acetate; 3.0 equiv of MSA, 2.0 vol of acetic acid, components added together at ambient temperature and heated in ARC.

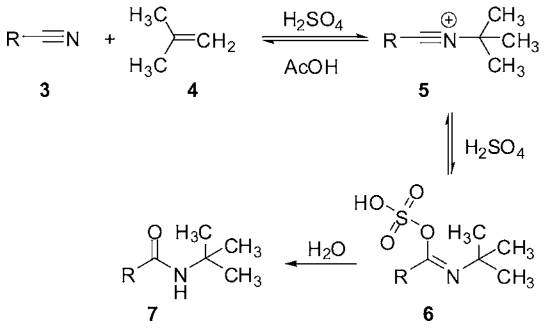
detection of acetic anhydride in the crude reaction mixture by GC analysis, they argued that acetic acid reacts with nitrilium ion **5** to generate acyl imidate **8**, then another equivalent of acetic acid reacts with acyl imidate **8** to generate amide **7** and acetic anhydride (**9**).

Under reaction conditions C, acetic anhydride was detected by in situ IR.[25] Additional control experiments proved acetic anhydride was not generated from background reactions of MSA with acetic acid or *tert*-butyl acetate.[26] Importantly, the acyl imidate **8** was not detected in any of the conditions investigated and is believed to be a short-lived intermediate which is immediately converted to amide **7**. These results corroborate the previous mechanistic studies reported by Jiang and Prasad, in which the quenching of a Ritter reaction with $Na^{18}OH$ failed to produce ^{18}O-enriched product.[3b]

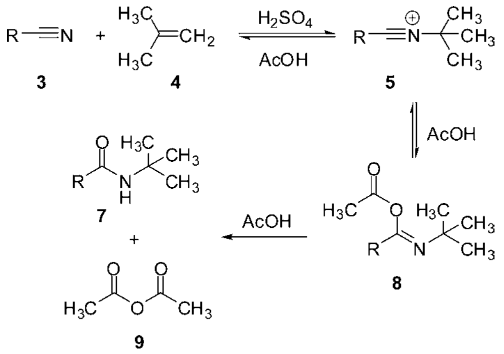
■ CONCLUSIONS

Three conditions for the Ritter reaction were investigated using *tert*-butyl acetate as the cation source. Employing *tert*-butyl acetate as the solvent and sulfuric acid created 22 L/kg of isobutylene. The "all-in" addition of sulfuric acid resulted in visible gas generation. Utilizing toluene as solvent and MSA created 17 L/kg isobutylene. Venting of the closed system at 45

Scheme 1. Ritter's originally proposed mechanism



Scheme 2. Glikmans et al. proposed mechanism generating acetic anhydride



°C produced a visible off-gas event. However, using acetic acid as solvent and MSA, very little isobutylene was produced (1 L/kg). Moreover, even the "all-in" addition of MSA and venting at elevated temperatures did not produce an off-gas event. The equilibrium between acetic acid and *tert*-butyl acetate is believed to buffer and control isobutylene emissions, resulting in lower operating pressures. These conditions have been conducted on large-scale in batch-processing mode.

■ EXPERIMENTAL SECTION

Ritter Reaction using *tert*-Butyl Acetate (neat) and Sulfuric Acid (30 min addition time). To a 1 L MP06 closed-system RC-1 calorimeter equipped with mechanical stirring, diaphragm pump, and DiComp fiber-optic probe (attached to a Mettler-Toledo ReactIR 4000) was charged 4-methoxybenzonitrile (45 g, 0.34 mol, 1.0 equiv) and *tert*-butyl acetate (171 mL, 3.8 vol) to form a light-brown slurry. The reactor was heated to 45 °C and the slurry dissolved to produce a light-brown, homogeneous solution. After thermal equilibration, an RC-1 heat flow calibration was performed (preaddition). Sulfuric acid (18 mL, 0.34 mol, 1.0 equiv) was charged by diaphragm pump over 33 min. After addition was complete, the reaction mixture was held to allow the heat flow to return to baseline, and an RC-1 heat flow calibration was performed. The reaction mixture was aged overnight at 45 °C. After the overnight age, the reactor vent was opened to observe for isobutylene off-gassing. The reactor was cooled to 20 °C and sampled for NMR analysis. In all experiments, the analytical data was in agreement with previously published data.[9]

Ritter Reaction using *tert*-Butyl Acetate (neat) and Sulfuric Acid ("all-in" addition). To a 1 L MP06 closed-system RC-1 calorimeter equipped with mechanical stirring, diaphragm pump, and DiComp fiber-optic probe (attached to a Mettler-Toledo ReactIR 4000) was charged 4-methoxybenzonitrile (45 g, 0.34 mol, 1.0 equiv) and *tert*-butyl acetate (171 mL, 3.8 vol) to form a light-brown slurry. After thermal equilibration at 20 °C, an RC-1 heat flow calibration was performed (preaddition). Sulfuric acid (18 mL, 0.34 mol, 1.0 equiv) was added in one portion, and the reactor was immediately sealed. The solution initially turned orange, followed by a dark greenish brown (*CAUTION: Gas bubbles observed during the initial exotherm!*). After addition was complete, the reactor was heated to 45 °C and aged overnight (*CAUTION: Gas bubbles observed during heating!*). Following the overnight age, the reactor vent was opened to observe for isobutylene off-gassing. The reactor was cooled to 20 °C, an RC-1 heat flow calibration was performed, and the crude reaction mixture was sampled for NMR analysis.

Ritter Reaction using Toluene, *tert*-Butyl Acetate, and MSA (3 h addition). To a 1 L MP06 closed-system RC-1 calorimeter equipped with mechanical stirring, diaphragm pump, and DiComp fiber-optic probe (attached to a Mettler-Toledo ReactIR 4000) was charged 4-methoxybenzonitrile (40 g, 0.30 mol, 1.0 equiv), toluene (144 mL, 3.6 vol), and MSA (19.5 mL, 0.90 mol, 3.0 equiv) to form a light-brown solution. The reactor was heated to 45 °C, and after thermal equilibration, an RC-1 heat flow calibration was performed (preaddition). *tert*-Butyl acetate (403 mL, 3.0 mol, 10.0 equiv) was charged by diaphragm pump over 3 h. After addition was complete, the reaction mixture was held to allow the heat flow to return to baseline, and an RC-1 heat flow calibration was performed. The reaction mixture was aged overnight at 45 °C. After the overnight age, the reactor vent was opened to observe for isobutylene off-gassing (***CAUTION: Violent off-gas event observed!***). The reactor was cooled to 20 °C, and the reactor vent was opened to observe for isobutylene off-gassing. The reactor was reheated to 45 °C, and the reactor vent was again opened to observe for isobutylene off-gassing (*CAUTION: Gas bubbles observed during venting!*). The reactor was cooled to 20 °C and sampled for NMR analysis.

Ritter Reaction using Acetic Acid, *tert*-Butyl Acetate, and MSA (40 min addition). To a 1 L MP06 closed-system RC-1 calorimeter equipped with mechanical stirring, diaphragm pump, and DiComp fiber-optic probe (attached to a Mettler-Toledo ReactIR 4000) was charged 4-methoxybenzonitrile (100 g, 0.75 mol, 1.0 equiv), acetic acid (100 mL, 1.0 vol), *tert*-butyl acetate (202 mL, 1.5 mol, 2.0 equiv) to form a light brown slurry. After thermal equilibration at 20 °C, an RC-1 heat flow calibration was performed (preaddition). A premixed solution of acetic acid (100 mL, 1.0 vol) and MSA (146 mL, 2.25 mol, 3.0 equiv) was charged by diaphragm pump over 40 min. After addition was complete, the reaction mixture was held to allow the heat flow to return to baseline, and a RC-1 heat flow calibration was performed. The reaction mixture was aged overnight at 20 °C. After the overnight age, the reactor vent was opened to observe for isobutylene off-gassing. The reactor was cooled to 20 °C and sampled for NMR analysis.

Ritter Reaction using Acetic Acid, *tert*-Butyl Acetate, and MSA ("All-In" Addition). To a 1 L MP06 closed-system RC-1 calorimeter equipped with mechanical stirring, diaphragm pump, and DiComp fiber-optic probe (attached to a Mettler-Toledo ReactIR 4000) was charged 4-methoxybenzonitrile (45 g, 0.34 mol, 1.0 equiv), acetic acid (90 mL, 2.0 vol), *tert*-butyl acetate (91 mL, 0.67 mol, 2.0 equiv) to form a light-brown slurry. After thermal equilibration at 20 °C, an RC-1 heat flow calibration was performed (preaddition). MSA (66 mL, 1.02 mol, 3.0 equiv) was added in one portion, and the reactor was immediately sealed. After addition was complete, the reaction mixture was held to allow the heat flow to return to baseline, and an RC-1 heat flow calibration was performed. The reaction mixture was aged overnight at 20 °C. In the morning, the mixture was heated to 45 °C, and the vent was opened to observe for isobutylene off-gassing. The reactor was further heated to 55 °C, and the reactor vent was opened for observing isobutylene off-gassing The reactor was cooled to 20 °C and sampled for NMR analysis.

■ ASSOCIATED CONTENT

S Supporting Information

General experimental methods, reference peak assignments, control experiments, and closed system calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Mr. Seth Huggins for assistance related to the IR spectrometry experiments, Mr. Mike Ronk for mass spectrometry analysis, and Dr. Matthew Bio for valuable discussions regarding the preparation of this manuscript. Ms. Jean Baum is acknowledged for assistance in development of the MSA/*tert*-butyl acetate/acetic acid conditions in support of the drug candidate program. Mrs. Jiemin Bao is acknowledged for development of the KF method for the determination of water content in strong acids. Dr. Margaret Faul, Dr. Robert Larsen, Dr. Jerry Murry, and Mr. Greg Sukay are gratefully acknowledged for support of this project.

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(6) For reviews, see: (a) Krimen, L. I.; Cota, D. L. *Org. React.* **1969**, *17*, 213−325. (b) Bishop, R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 6, pp 261−300. (c) Kürti, L.; Czakó, B. *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier Academic Press: New York, 2005; pp 382−383.

(7) "Volatile Organic Compounds" per definition CFR Part 51.100 (s). Isobutylene boiling point = 6.9 °C, flash point = −80 °C (closed cup).

(8) Chang, S.-J. *Org. Process Res. Dev.* **1999**, *3*, 232−234 and references cited therein.

(9) Baum, J. C.; Milne, J. E.; Murry, J. A.; Thiel, O. R. *J. Org. Chem.* **2009**, *74*, 2207−2209.

(10) (a) Brandt, J. C.; Elmore, S. C.; Robinson, R. I.; Wirth, T. *Synlett* **2010**, *20*, 3099−3013. (b) "Thermodynamic runaways" during batch processing was specifically cited as a concern.

(11) Sulfuric acid was initially reported with these conditions (see reference 9). However, MSA was selected for future development due to low water content and improved impurity profile. Details will be disclosed in a separate publication.

(12) An MP06, 1 L, 6 bar pressure-rated calorimeter was utilized for all studies. Solutions were charged into the closed system using a diaphragm pump.

(13) See Supporting Information for reference peak assignment and IR spectra.

(14) The calculation of pressure from the addition of a liquid into a closed system is based on the compression of the headspace inside the system. In our experiments, the headspace was air (headspace not purged prior to each experiment); thus, the Ideal Gas Law can be used for the calculation of pressure; see Supporting Information for calculations. For the purposes of comparison between conditions, isobutylene was assumed to be an ideal gas. Isobutylene evolution was calculated on the basis of closed system pressure and does not include amount lost during venting.

(15) It should be noted that the heat of reaction for the two examples listed for conditions A should be similar. We believe that the heat of reaction for the "all-in" condition is lower due to the lower reaction temperature (25 °C vs 45 °C for the dosed conditions), the possible loss of isobutylene through the open port during the addition (an evaporative effect), and a reaction that was potentially incomplete (mixture was heated to 45 °C to ensure reaction completion).

(16) RC-1 data was adjusted accordingly to remove the contribution from heat of dosing.

(17) All ARC experiments were conducted utilizing magnetic stirring. ARC analysis of the reagents/solvent (nitrile absent) did not show exothermic activity up to 150 °C. See Supporting Information for ARC analysis.

(18) We note that large temperature fluctuations could possibly influence the observed IR trends due to the thermal dependence of infrared absorptions.

(19) (a) Dias, E. L.; Hettenbach, K. W.; am Ende, D. J. *Org. Process Res. Dev.* **2005**, *9*, 39−44. (b) It should be noted that the presence of methanol was shown to terminate the scrubbing ability of the system.

(20) We believe the heat of reaction is lower for these conditions, when compared to the MSA/acetic acid conditions, because there is no heat of mixing between MSA and acetic acid.

(21) The heat spike postaddition is an artifact of the dosing method, rather than an actual kinetic effect.

(22) Bomb contents were analyzed by ^{1}H NMR after exothermic activity. ARC analysis of the reagents/solvent showed a 1 °C exotherm at 130 °C; however, it was not of the same magnitude of the real system. See Supporting Information for ARC analysis.

(23) Conditions utilized for manufacturing were slightly modified from reference 9 (equivalents, solvent volume). Details will be disclosed in a separate publication.

(24) Glikmans, G.; Torck, B.; Hellin, M.; Coussemant, F. *Bull. Soc. Chim. Fr.* **1966**, *4*, 1376−1386.

(25) (a) The acetic anhydride peak assignment was confirmed by charging acetic anhydride into the crude reaction mixture. (b) The use of MSA resulted in lower water content. Adding 1.0 equiv water to conditions C resulted in no detection of acetic anhydride by IR.

(26) Further processing and examination of IR data, including derivitization and principal component analysis failed to identify acylimidate intermediates of type **8** in all experiments.