

# Development and Scale Up of a Route to Cyclohexylhydrazine Dimethanesulfonate

Terrence J. Connolly,\* Andrew J. Crittall, Alkarim S. Ebrahim, and Guijun Ji

Raylo Chemicals Inc., A Laporte Fine Chemicals Company, 8045 Argyll Road, Edmonton, Alberta, T6C 4A9 Canada

## Abstract:

A mild, high-yielding synthesis of cyclohexylhydrazine dimethanesulfonate has been developed that is suitable for further scale up. The process consists of three chemical steps: condensation of cyclohexanone with *tert*-butyl carbazate, reduction of the hydrazone carboxylate to a hydrazine carboxylate with borane–THF, and hydrolysis, decarboxylation, and derivatization with methanesulfonic acid. From studies using a reaction calorimeter, it was determined that the last stage of the process occurs in two discrete steps, requiring 2 equiv of methanesulfonic acid. The first equivalent of acid is consumed by N-protonation. Deprotection of the Boc group occurs with the second equivalent of acid, as evident by the gas evolution. The heat of reaction for the acid addition was determined to be 57.7 kJ/kg and represents an adiabatic temperature rise of 27.4 °C.

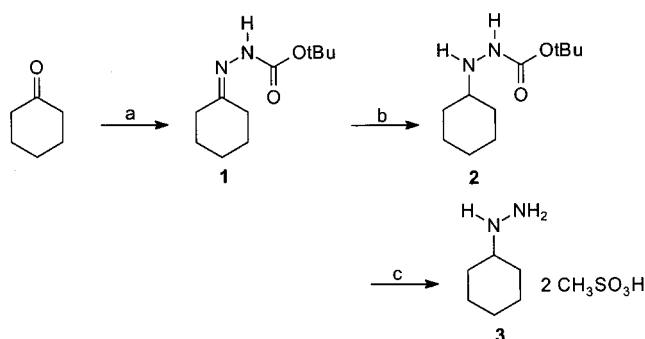
## Introduction

The use of hydrazines as building blocks in the synthesis of several heterocyclic systems is well documented.<sup>1</sup> In connection with a project under development, we required significant amounts of cyclohexylhydrazine. Therefore, we were interested in developing a route that would generate a hydrazine derivative amenable to large-scale production and long-term storage. This paper discusses our efforts towards this goal.

A survey of the literature revealed several routes for the synthesis of alkylhydrazines.<sup>2–7</sup> One approach involves condensation of methyl or ethyl carbazate with a carbonyl compound, followed by hydrazone reduction, hydrolysis, and decarboxylation. This method is not compatible with glass-lined vessels due to the high temperature and strongly basic conditions used for the hydrolysis and decarboxylation. Additionally, there are reports of this method suffering from sporadic yields and the formation of by-products that are difficult to remove.<sup>3,5</sup>

Venton improved the above-mentioned process by using *tert*-butyl carbazate rather than methyl or ethyl carbazate.<sup>5</sup> This modification allowed the hydrolysis to be performed

## Scheme 1<sup>a</sup>



<sup>a</sup> Key: (a) *tert*-Butyl carbazate, hexanes, Δ; (b) H<sub>3</sub>B:THF, Na<sub>2</sub>CO<sub>3</sub>/NaCl/H<sub>2</sub>O; (c) CH<sub>3</sub>SO<sub>3</sub>H, PhMe/THF.

under acidic conditions. Precipitation of the hydrazine as a salt occurred concomitantly, and by-product formation was not observed. Although the isolation methods and work-ups developed by Venton were not particularly well-suited for an industrial synthesis, his route was an attractive starting point for process development. The process we developed is shown in Scheme 1.

## Results and Discussion

**Stage One: Hydrazone Formation.** Our initial laboratory trials utilized heptane as the reaction solvent rather than hexane as suggested by Venton. We reasoned that the higher boiling point (98 vs 69 °C) of heptane versus hexane would lead to a shorter reaction time. Heptane's higher conductivity ( $3 \times 10^{-2}$  vs  $1 \times 10^{-5}$  pS m<sup>-1</sup>) was also attractive. Although all processing equipment in our plants is grounded, safety and hazards considerations dictate that the use of non-conductive solvents be limited, especially when heterogeneous mixtures are present. High levels of electrostatic charge can be generated during a solid/liquid-phase separation. Insulating solvents can retain an electrostatic charge for long periods of time, even when in contact with a grounded surface.

Using heptane as the process solvent worked well, providing the product hydrazone **1** in a yield of 80–85%. However, the yield of **1** dropped from 85% to 54% when the reaction time was increased from 4 to 16 h, indicating product instability. Suspending pure, dry **1** in heptane and agitating the resultant slurry under reflux conditions verified product decomposition. Product recovery was only 85% after 5 h at reflux in heptane.

Hexanes was then evaluated as a reaction solvent on the assumption that product decomposition was temperature-dependent. Rapid conversion to the desired hydrazone

\* Author for correspondence. Telephone: (780) 468-6060. Fax: (780) 468-4784. E-mail: terry.connolly@raylo.laporteplc.com.

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occurred at reflux following suspension of *tert*-butyl carbamate and a slight excess of cyclohexanone in hexanes. The reaction was complete within 3 h, and afforded product in an average yield of 95%. Increasing the reaction time to 16 h caused the yield to decrease to 90%, which was significantly better than the 54% yield observed after an equivalent reaction time in heptane.

The conductivity issue mentioned earlier was addressed by adding *iso*-propyl alcohol (10% w/w, relative to hexanes) to the slurry prior to filtration. The presence of *iso*-propyl alcohol did not adversely affect product recovery. Additionally, the use of the more volatile hexanes rather than heptane allowed us to dry hydrazone **1** on the filter to the point where it contained less than 5% residual solvent (wt/wt basis). This removed a drying step, further simplifying the operability of the process since the amount of residual solvent that would be carried forward to the next stage was negligible.

**Stage Two: Hydrazone Reduction.** Although Venton's procedure of adding a solution of borane–tetrahydrofuran directly to the solid hydrazone would work on a small scale, we found it more practical to suspend the hydrazone in THF prior to charging the borane solution. Agitation of the hydrazone slurry prior to the borane addition resulted in a more even distribution of the borane solution as it was charged. Adding a cold (5–10 °C) solution of the borane complex and adjusting the addition rate to maintain the reaction temperature controlled the exotherm of the reaction.

When the reduction was deemed complete, an aqueous solution of sodium carbonate and sodium chloride was added. This salt mixture quenched the residual borane complex, extracted the boric acid into the aqueous layer, and led to an organic layer that contained only 6% water (Karl-Fisher method). Quenching the reaction with a solution of sodium carbonate alone, followed by washing the organic layer with a brine solution, was not effective in lowering the water content of the organic layer. Decreasing the water content was desirable since the final product, an ionic salt, was suspected to have some water solubility. As well, we had observed slow gas evolution from stock solutions of **2**, which was attributed to hydrolysis of the Boc group.

Following the aqueous work-up, the THF stock solution of **2** was distilled under reduced pressure. One co-evaporation with toluene, followed by dilution to the desired concentration, afforded a stock solution of hydrazinocarboxylate **2** containing 1.5% water (Karl-Fisher method) that could be carried forward directly to the final stage of the process.

**Stage Three: Hydrolysis, Decarboxylation, and Derivatization.** Having developed a process that minimized the amount of water carried forward to the final stage of the process, we believed that using aqueous HCl as suggested by Venton would result in a reduced yield of product. It was determined that even use of concentrated HCl led to significant product loss to the filtrate due to the water present in the acid. It was anticipated that use of anhydrous HCl would alleviate the problem of product loss to the mother liquor. Addition of dry HCl to solutions of **2** in toluene or heptane led to an exotherm that was difficult to control.

Additionally, the isolated product was a very non-granular, pasty solid that was slow to filter, dried poorly, and entrained a significant amount of HCl. Although a variety of solvents and solvent mixtures were examined, the filterability of the hydrazine salt was not improved.

A survey of other proton sources and solvents indicated that methanesulfonic acid led to a derivative that filtered well when 10% THF in toluene (wt/wt basis) was used as the process solvent. Although using 1 equiv of methanesulfonic acid led to poor recoveries, increasing the charge to 2 equiv resulted in precipitation of the product as dimesylate salt **3** in excellent yield. The use of THF as a co-solvent was an important parameter since product **3** filtered poorly when isolated from neat toluene.

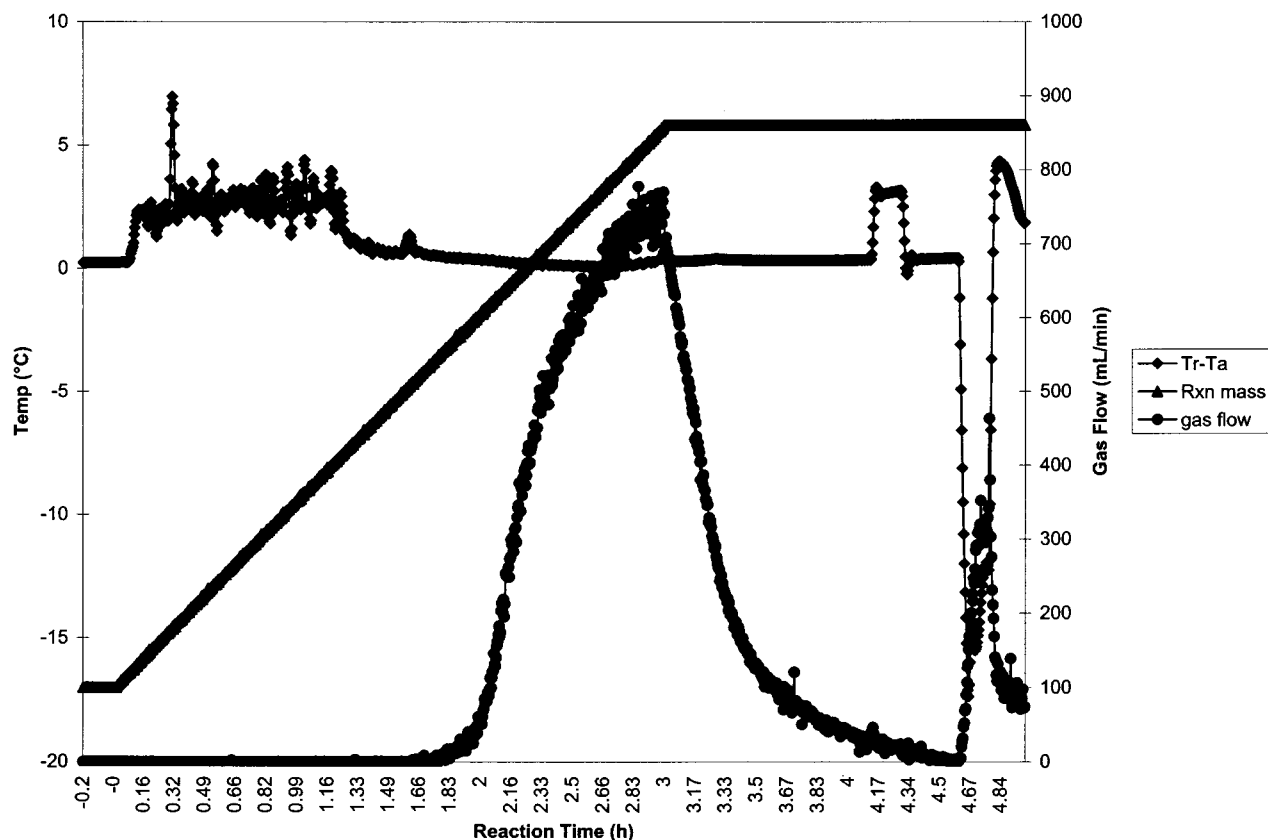
Although the process afforded good quality product **3** in an overall yield of 90%, gas evolution did not appear to be proportional to the dose of methanesulfonic acid. Initial lab trials indicated that off-gassing did not start until the addition of methanesulfonic acid was ~30% complete. Increasing the reaction temperature did not lead to an earlier onset of gas evolution. If the reaction was showing an induction time, or had mass flow characteristics that were not addition controlled, then further scale up would be approached cautiously. With a process that generated 2 equiv of gas per 1 equiv of substrate, then factors such as vessel size, reactor headspace, rating of the bursting disk, and vent design would need to be considered carefully prior to scale up. On the basis of these concerns, a reaction calorimeter study was done on stage three of the process.

**Reaction Calorimeter Study.** Our concerns with stage three centered on the observation of an exotherm and the generation of significant quantities of isobutylene and carbon dioxide. An experiment was conducted using a Mettler Toledo RC1e calorimeter to establish the heat and mass flow characteristics of stage three. In this experiment, 2 equiv of methanesulfonic acid were added via a dosing loop to a solution of **2** in THF/toluene. The addition of acid occurred over 3 h while the calorimeter operated in a mode that maintained the pot temperature at 25 °C.

The key data collected from the calorimeter study are shown in Figure 1. The series labeled (Tr-Ta) represents the difference between the pot temperature and the jacket temperature. A positive value indicates that cooling was applied to the reactor to offset a temperature rise due to an exothermic reaction.

Figure 1 shows that the reaction was exothermic only during the addition of the first equivalent of acid. After 1 equiv of acid was charged, the exotherm ceased, and gas evolution started. Gas evolution steadily increased until it reached a maximum that corresponded with the end of the acid addition and then decreased immediately. When the gas evolution was negligible, the reactor contents were adjusted to 40–50 °C, and gas evolution was observed again. This was attributed to dissolved gases, but the possibility exists that the reaction did not go to completion until this extra heating period was introduced.

The results of the calorimeter study were in conflict with the observations made when this stage was conducted in a



**Figure 1.**

20 L reactor. During lab trials, gas evolution was observed after ~30% of the acid had been added, whereas during the calorimeter study, gas evolution started after 50% of the acid had been added. The major difference between the two trials was the time required for the methanesulfonic acid charge. During the lab scale up, we charged 1.2 kg of acid over a period of 3.5 h. When the experiment was conducted in the calorimeter, 0.3 kg of acid was charged over 3 h. We believe that the different feed rate of methanesulfonic acid was responsible for the different observations made.

The calorimeter data indicates that the reaction occurred in two discrete stages. Protonation of the nitrogen, which was an exothermic reaction, occurred first. Once the first equivalent of acid was consumed, then cleavage of the *t*-Boc group occurred, as evident by the evolution of gas during the charging of the second equivalent of methanesulfonic acid. No exotherm is observed during the charge of the second equivalent of acid, presumably because it is masked by the endotherm associated with the generation of 2 equiv of gas.

On the basis of our studies, it appears that rapid addition of methanesulfonic acid resulted in some accumulation of acid. Although it is possible that the first protonation step is slow, it is more likely that slow diffusion of the acid through the reaction mixture resulted in a localized accumulation that allowed the hydrolysis and decarboxylation to occur before all of **2** had been protonated.

One important observation from the calorimeter study was that both the exotherm and gas evolution were proportional to the dose of methanesulfonic acid. With respect to further

scale up, this addition control of both pot temperature and pressure are attractive features of this process.

## Conclusions

A simple, high-yielding, streamlined process has been developed for the large-scale preparation of a dimethanesulfonate salt of cyclohexylhydrazine. Key points in the development were the use of hexanes as a solvent for stage one, which resulted in a robust hydrazone-forming process. Suspension of the hydrazone in THF, followed by addition of borane–THF resulted in the smooth formation of the stage two hydrazino carboxylate. The aqueous work up removed boron residues and afforded an organic layer that could be dried azeotropically during the solvent switch from THF to toluene. Finally, a reaction calorimeter study provided detailed information with respect to the reaction mechanism, mass, and energy flow of the final stage of the process. It was determined that both the exotherm and gas evolution of the last stage were proportional to acid dose. Control of both the reaction temperature and reactor pressure would be easily achieved upon further scale up by adjusting the acid feed rate.

## Experimental Section

*tert*-Butyl carbazate (800 g, 6.05 mol, 1.0 equiv.), cyclohexanone (713 g, 1.2 equiv), and hexanes (2.0 kg) were charged to a 10 L reactor. The resulting slurry was heated to reflux, and water was removed via a Dean–Stark trap. After 3.5 h at reflux, TLC (3% MeOH in DCM, phosphomolybdic acid (PMA) dip and char for visualization)

indicated that the reaction was complete. The slurry was cooled to 0–5 °C and agitated for ~1 h, and 2-propanol (0.2 kg) was added. The slurry was filtered and the reactor rinsed forward with the filtrate until free of solids. The filter cake was pulled dry for ~30 min and then discharged to yield 1.26 kg of hydrazone **1** (98.4% of theory). The hydrazone was charged to a 20 L reactor, followed by 1.26 kg of THF to affect a slurry. Agitation was started and borane–THF (1.0 M in THF, 6.52 kg, 1.2 equiv) was added over ~1 h. As the reaction progressed, the slurry became a clear homogeneous solution. Over the course of the addition, a temperature rise of 15 °C was noted (start temp = 16 °C, final = 31 °C), no external cooling was applied. The solution was then adjusted to 40–60 °C for 1 h, then cooled to 20 °C. A solution of Na<sub>2</sub>CO<sub>3</sub> (770 g, 1.2 equiv) and NaCl (707 g, 2.0 equiv) in water (6.93 kg) was slowly charged (**Caution: Strong gas evolution in the beginning**) and the resulting bi-phasic solution was agitated at room temperature for 1 h. The layers were separated, and the organic layer was concentrated under reduced pressure until distillation stopped. Toluene (1.9 kg) was charged to the slurry and the vacuum distillation repeated (maximum pot temperature 43 °C). Toluene (2.88 kg) and THF (320 g) were charged to the residue, and the contents were adjusted to 20 °C. Methanesulfonic acid (1.16 kg, 2.0 equiv) was added over 3.5 h (**Caution: Exotherm and strong gas evolution**) during which time there was an exotherm of 21 °C. After the addition, the reaction mixture was adjusted to 40 °C until gas evolution ceased. The slurry was then cooled to 0–5 °C, agitated for 1–2 h, and filtered, rinsing the reactor forward with the filtrate. When all of the solids were rinsed from the reactor, the reactor and cake were rinsed twice with 10% THF/toluene (250 mL each). The cake was pulled as dry as possible and then discharged, yielding 2.41 kg of the product as a wet cake. A sample of the cake was analyzed for loss on drying, and the corrected yield of the dimesylate was determined to be 89.7% from *tert*-butyl carbazate (31% LOD).

**Reaction Calorimeter Experiment.** Toluene (1200 g) and THF (83 g) were charged to a Mettler Toledo RC1e,

which was equipped with a pH probe, pot temperature sensor, glass baffles, a down-flow propeller agitator, a calibration heater, gas flowmeter, and a dosing pump with dosing tip sensor. The agitation was ramped from 100 to 650 rpm over 5 min. Cyclohexylhydrazine carboxylate (300 g) was charged to the reactor, the temperature was adjusted to 25 °C, and a calibration was performed to determine the heat-transfer coefficient. Methanesulfonic acid (305 g) was added via a dosing loop over 3 h. At the end of the addition when gas evolution had subsided, the temperature was increased to 45 °C at a rate of 2 °C/min. The contents were held at that temperature until the flow of off-gas decreased (~15 min) and then were cooled to 5 °C prior to discharging the reactor contents. The RC-1 was interfaced with a Dell P11233 computer, and all data were collected and analyzed using the WinRC software package.

**Product Characterization.** *tert*-Butyl cyclohexylidene hydrazinocarboxylate (**1**): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz) 1.46 (s, 9H), 1.60 (m, 6H), 2.19 (t, *J* = 6.20 Hz), 2.32 (t, *J* = 6.20 Hz), 7.57 (s, 1H); mp 136.4–136.7 °C, lit. 134–135 °C.<sup>5</sup>

*tert*-Butyl cyclohexylhydrazinocarboxylate (**2**): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz) 1.15 (m, 6H), 1.45 (s, 9H), 1.75 (m, 5H), 2.75 (m, 1H), 6.10 (br, 1H) ppm; mp 80.5–81.7 °C, lit. 76–78 °C.<sup>8</sup>

Cyclohexylhydrazine dimethansulfonate (**3**): <sup>1</sup>H NMR (DMSO, 200 MHz) 1.10 (m, 6H), 1.75 (m, 4 H), 2.40 (s, 6H), 2.85 (m, 1H), 8.65 (br, 5H) ppm. Elemental analysis: Calcd (found): 31.36 (29.28) %C, 7.24 (7.13) %H, 7.99 (9.14) %N, 20.93 (19.21) %S.

#### Acknowledgment

We are grateful to Dr. Robin Nicol for his critical review of this manuscript and to the reviewers for their constructive comments.

Received for review July 13, 2000.

OP0002904

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