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2-Bromo-3-(cyclohexyloxy)acrylaldehyde: An Isolable Enol Ether of Bromomalonaldehyde Suitable for Use in the Manufacture of Imidazolecarboxaldehydes[†]

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Abstract:

Enol ethers derived from 2-bromomalonaldehyde are useful intermediates for the preparation of functionalized imidazolecarboxaldehydes. Recent work in our group required that bromomalonaldehyde be converted to an enol ether on a large scale and be used in a campaign to generate a late-stage intermediate in the synthesis of an investigational active pharmaceutical ingredient (API). 2-Bromomalonaldehyde was converted into several enol ethers and each was evaluated with respect to its suitability for long-term storage and the temperature at which thermal decomposition was initiated. Although the highest onset temperature was measured with the ethyl enol ether (178 °C), the cyclohexyl enol ether was discovered to be an isolable solid (mp 66.5 °C). Other enol ethers examined in our hands could not be isolated as solids and storage as stock solutions did not offer the long-term stability required to support our campaign. A process safety hazards analysis revealed that the most potential for a hazardous event to occur was during the solvent exchange from processing solvent to isolation solvent. The total energy released during decomposition at this point would have exceeded the emergency vent relief capacity of the reactor set. The final concentration of reagent in solvent was adjusted so that the remaining solvent would function as a heat sink and diluent should decomposition occur, ensuring that the process did not exceed available vent relief capacity. The chemistry detailed in this communication was scaled up and produced a total of 1.1 MT of 2-bromo-3-(cyclohexyloxy)acrylaldehyde in four batches. Batch sizes ranged from 200 − 330 kg and the average yield was 80%.

Introduction

Enol ethers of bromomalonaldehyde find utility in organic synthesis owing to their ability to undergo a double addition followed by an elimination to generate functionalized imidazolecarboxaldehydes when combined with amidines. Such functionalized imidazolecarboxaldehydes have proven useful in the synthesis of a number of investigational active pharmaceutical ingredients (API) including potential antibiotics,[1−10] as well as compounds with the potential to treat a variety of other indications.[11−24] Recent work in our group required that such a sequence be scaled up to a pilot plant and in the course of our development work, we had the opportunity to examine a series of enol ether derivatives of bromomalonaldehyde.

Examination of the literature revealed that several enol ether derivatives of 2-bromomalonaldehyde have been reported,

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(1) Abe, T.; Matsunaga, H.; Mihira, A.; Sato, C.; Ushirogochi, H.; Sato, K.; Takasaki, T.; Venkatesan, A.; Mansour, T. WO/2003/093277, Nov. 13, 2003.

(2) Abe, T.; Matsunaga, H.; Mihira, A.; Sato, C.; Ushirogochi, H.; Sato, K.; Takasaki, T.; Venkatesan, A.; Mansour, T. U.S. Pat. 2004132708, July 8, 2004.

(3) Kremer, K. A. M.; Krishnan, L.; Venkatesan, A. M.; Jennings, M.; Zeldis, J.; Abe, T.; Mansour, T.; Strong, H. WO/2009/006243, Jan. 8, 2009.

(4) Mansour, T. S.; Venkatesan, A. M. WO/2006/130588, Dec. 7, 2006.

(5) Mansour, T. S.; Venkatesan, A. M. U.S. Pat. 2006276446, Dec. 7, 2006.

(6) Mansour, T. S.; Venkatesan, A. M.; Bradford, P.; Petersen, P. J.; Projan, S. J. WO/2007/016134, Feb. 8, 2007.

(7) Venkatesan, A.; Agarwal, A.; Abe, T.; Ushirogochi, H.; Takasaki, T.; Mihira, A.; Mansour, T. S. *ChemMedChem* **2008**, *3*, 1658–1661.

(8) Venkatesan, A. M.; Agarwal, A.; Abe, T.; Ushirogochi, H.; Yamamura, I.; Kumagai, T.; Petersen, P. J.; Weiss, W. J.; Lenoy, E.; Yang, Y.; Shlaes, D. M.; Ryan, J. L.; Mansour, T. S. *Bioorg. Med. Chem.* **2004**, *12*, 5807–5817.

(9) Venkatesan, A. M.; Mansour, T. S.; Abe, T.; Yamamura, I.; Takasaki, T.; Agarwal, A.; Santos, O. D.; Sum, F.-W.; Lin, Y.-I. WO/2003/093279, Nov. 13, 2003.

(10) Venkatesan, A. M.; Mansour, T. S.; Abe, T.; Mihira, A.; Agarwal, A.; Ushirogochi, H.; Gu, Y.; Tamai, S.; Sum, F.-W. WO/2003/093280, Nov. 13, 2003.

(11) Arrhenius, T.; Chen, M.; Cheng, J. F.; Haramura, M.; Huang, Y.; Nadzan, A.; Tith, S.; Wallace, D.; Zhang, L.; Brown, S.; Harmon, C. WO/2002/058690, Aug. 1, 2002.

(12) Cheng, J.-F.; Chen, M.; Liu, B.; Hou, Z.; Arrhenius, T.; Nadzan, A. M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 695–700.

(13) Cogan, D.; Hao, M.-H.; Kamhi, V. M.; Miller, C. A.; Netherton, M. R.; Swinamer, A. D. WO/2005/090333, Sep. 29, 2005.

(14) Dagger, R. E. WO/1995/32189, Nov. 30, 1995.

(15) Edwards, L.; Isaac, M.; Johansson, M.; Kers, A.; Malmberg, J.; McLeod, D.; Mindis, A.; Staaf, K.; Slassi, A.; Stefanac, T.; Stormann, T.; Wensbo, D.; Xin, T.; Arora J. U.S. Pat. 2005272779, Dec. 8, 2005.

(16) Gerlach, K.; Priepke, H.; Wienen, W.; Schuler-Metz, A.; Dahmann, G.; Nar, H. WO/2008/135526, Nov. 13, 2008.

(17) Gerlach, K.; Priepke, H.; Wienen, W.; Schuler-Metz, A.; Dahmann, G.; Nar, H. WO/2008/116881, Oct. 2, 2008.

(18) Luke, G. P.; Maynard, G.; Mitchell, S.; Thurkauf, A.; Xie, L.; Zhang, L.; Zhang, S.; Zhao, H.; Chenard, B. L.; Gao, Y.; Han, B.; He, X. S. WO/2003/082829, Oct. 9, 2003.

(19) Mokhallalati, M. K.; Pridgen, L. N.; Shilcrat, S.; Weinstock, J. WO/1994/06776, Mar. 13, 1994.

(20) Shilcrat, S. C.; Mokhallalati, M. K.; Fortunak, J. M. D.; Pridgen, L. N. *J. Org. Chem.* **1997**, *62*, 8449–8454.

(21) Thurkauf, A.; He, X.-S.; Zhao, H.; Peterson, J.; Zhang, X.; Brodbeck, R.; Krause, J.; Maynard, G.; Hutchison, A. U.S. Pat. 6,723,743, Apr. 20, 2004.

(22) Thurkauf, A.; Zhang, X.; He, X.-S.; Zhao, H.; Peterson, J.; Maynard, G.; Ohliger, R. WO/2002/049993, Jun. 27, 2002.

(23) Veverka, M.; Kriz, M.; Veverkova, E.; Bartovic, A.; Putala, M.; Jordan, B. K. WO/2007/003280, Jan. 11, 2007.

(24) Wang, Y.; Li, Y.; Li, Y.; Zheng, G.; Li, Y. WO/2006/081807, Aug. 10, 2006.

10.1021/op100156y

including R = Me, Et, *i*-Pr, *n*-Pr, and *n*-Bu (**2a** to **2e**). The majority of reports detailing the use of these intermediates have focused on the isopropyl derivative **2c**. Presumably, this bias was impacted by the pioneering work of Shilcrat who concluded that **2c** offered the best results in terms of long-term stability and yield of imidazole on the basis of the screening work performed in that laboratory.[20]

Recent work in our group required large amounts of an enol ether derivative of **1**, and our initial efforts focused on using the isopropyl analogue. Shilcrat reported that the enol ether derivatives were readily prepared using bromomalonaldehyde with catalytic acid and the required alcohol and azeotropic removal of water in the recommended solvents of chloroform or cyclohexane. During preliminary safety screening, it was discovered that performing the azeotropic removal of water at atmospheric pressure in cyclohexane did not offer the required safety margin between the reaction temperature and the onset to decomposition. Multiple solutions to this problem were evaluated, but each suffered a different drawback. If a low-boiling solvent was used to meet the required safety margin during the reaction, another solvent exchange would be required to telescope the process forward.[25] An attempt to use the downstream solvent (THF) as the solvent for formation of the enol ether and telescope the stock solution forward was not successful because the efficiency of the azeotrope with water was low and IPA codistilled with the THF. However, a greater concern was the long-term stability of the intermediate enol ether in solution. The campaign that was in the planning stages was going to require the generation of approximately 1 MT of **2e** so that preparing and storing this quantity of material would be challenging.

Results and Discussion

In light of the aforementioned challenges, we decided to re-evaluate other enol ethers, hoping to succeed on two fronts: identify a compound that had a higher onset to decomposition to provide a greater operating window and identify an intermediate that was isolable.[26] A summary of the compounds we prepared and selected TSU safety data is shown in Table 1.[27]

From our evaluation, the most notable compounds were **2b**, which had the highest onset to decomposition, and **2f**, which was easily isolated at the end of the reaction as a solid. The latter feature was deemed more valuable than the slightly higher onset temperature and **2f** was selected as the candidate to be scaled up. The solubility of **2f** was determined in a number of nonpolar solvents in an attempt to develop a direct-drop process (Table 2).[28]

Table 1. **Summary of thermal screening unit (TSU) data for various enol ether derivatives**

compound	onset temperature (°C)	notes: TSU observation relative to severity of thermal decomposition
1	105	max $\mathrm{d}T/\mathrm{d}t$ 80 °C/min max $\mathrm{d}P/\mathrm{d}t$ 115 bar/min residual pressure: 20 bar
2a (R = Me)	110	max $\mathrm{d}T/\mathrm{d}t$ 253 °C/min max $\mathrm{d}P/\mathrm{d}t$ 3514 bar/min residual pressure: 35 bar
2b (R = Et)	178	max $\mathrm{d}T/\mathrm{d}t$ 92 °C/min max $\mathrm{d}P/\mathrm{d}t$ 650 bar/min residual pressure: 16 bar
2c (R = *i*-Pr)	105	max $\mathrm{d}T/\mathrm{d}t$ 140 °C/min max $\mathrm{d}P/\mathrm{d}t$ 4045 bar/min residual pressure: 40 bar
2f (R = c-Hex)	135	max $\mathrm{d}T/\mathrm{d}t$ 118 °C/min max $\mathrm{d}P/\mathrm{d}t$ 211 bar/min residual pressure: 8 bar melting point: 66.5 °C

Table 2. **Solubility of 2f in various solvents and solvent mixtures**

solubility (mg/mL)					
heptane (10 °C)	heptane (95 °C)	cyclohexane (22 °C)	1:1 heptane/ cyclohexane (22 °C)	octane (22 °C)	toluene (22 °C)
6.9	35.2	25.4	10.1 mg/mL	4.1 mg/mL	>380 mg/mL

Table 3. **Summary of lab-scale experiments for the conversion of 1 to 2f**

scale (g of **1**)	reaction solvent	isolation solvent	product yield (%)	product purity (wt %)	losses to ML (% of yield)
180	toluene	heptane	94	95	<1
50	cyclohexane	cyclohexane/ heptane	73	95	6
50	methylene chloride	heptane	88	95	2
239[a]	toluene	octane	81	95	n/d

[a] A 940-mL sample from a pilot-scale batch was worked up in the lab; the batch used 269 kg of **1** and had a volume of 1060 L when sampled. For comparison, the large-scale batch gave 79% yield of 96.6 wt % pure product.

The low solubility in heptane indicated that it should be the solvent for isolation.[29] Unfortunately, attempts to use it as the processing solvent led to poor conversion and formation of a sticky mass that was difficult to stir, even at elevated temperatures. Losses to the mother liquors would be too high when cyclohexane was used as the reaction and isolation solvent. The assay yield of product was also lower when the reaction was performed in cyclohexane; thus, isolation from a mixture of cyclohexane/heptane provided a significantly lower yield than isolation from heptane (see Table 3).

Although excellent results were achieved when the reaction was conduced in methylene chloride and the product isolated from heptane, our Pilot Plant had strict limits on the use of methylene chloride.[30] In light of the volume of methylene

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(25) The greatest safety concern occurred during the solvent exchange that would be required at the end of the reaction when the product-containing stream was concentrated to a low volume during the exchange.

(26) The methyl ether, prepared using diazomethane, was reported to have a melting point of 56−57 °C. See: Shostakovskii, M. F.; Kuznetsov, N. V.; Yang, C.-M. *Bull. Acad. Sci. USSR (Engl. Trans.)* **1961**, 1570−1572, DOI: 10.1007/BF00906156.

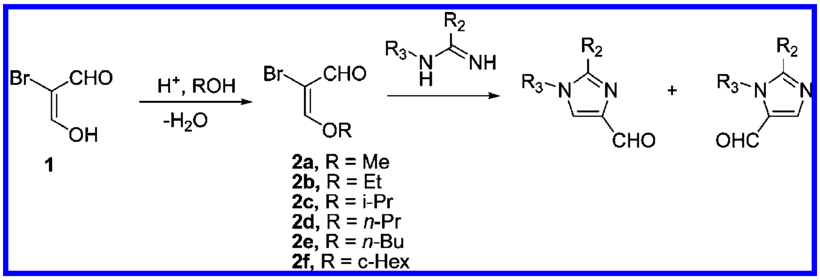
(27) These data were generated using a thermal safety unit (TSU) from HEL. It is important to point out that ARC test results often give lower onset temperatures. In the case of **2f**, ARC results suggest that a thermal onset temperature as low as 88 °C may occur with 50 wt % solutions.

(28) Chen, C.-K.; Singh, A. K. *Org. Process Res. Dev.* **2001**, *5*, 508–513.

(29) The solubility of **2f** in octane was not performed during the preliminary solvent screening. It was only investigated after the pilot-plant batch was underway, and we were able to evaluate on-scale the amount of heptane required for the solvent exchange.

(30) Methylene chloride is the safest solvent from a process safety perspective since it offers a large evaporative barrier between the reaction temperature and the onset to decomposition.

Scheme 1. **Preparation of enol ethers from bromomalonaldehyde and conversion to imidazolecarboxaldehydes**



chloride that would be required to generate the target quantity of **2f**, toluene was selected as the solvent for the pilot-plant batches.[31] The process was run under a partial vacuum in order to lower the reflux temperature to 45−55 °C to ensure that a sufficient margin existed between the operating temperature and the onset to decomposition.[32]

The supplier of cyclohexanol offered material with water added to suppress the melting point making it easier to handle on-scale. We have successfully run the conversion of **1** to **2f** with up to 10 wt % water added (relative to cyclohexanol) without any detrimental impact on the yield or quality of isolated product. The reaction mixture started as a slurry, but gradually became a clear solution and remained as such throughout the rest of the reaction. Fresh toluene was added to the reaction mixture as distillate was being collected so the reaction volume remained essentially constant. On a lab sale (180 g of **1**), the reaction required approximately three hours to be complete, as judged using HPLC (**1** <3%). In-process monitoring demonstrated that two peaks with the same mass as the product were formed, presumable **2f** and the geometric isomer, with area-normalized percentages of 90.9 and 1.7 respectively. An impurity was formed during the reaction that was present during in - process monitoring at levels up to 8%, but this impurity was effectively purged during the crystallization so was not identified.

Once the reaction was deemed complete, the reaction mixture was concentrated to a low volume and diluted with heptane. The concentration/dilution sequence was repeated until the level of weight percent of toluene in heptane was 2−10%. At the low end of the range, oiling out of the product was sometimes observed in the lab at temperatures below 40 °C, although even in these cases, the oil did eventually turn over to form an acceptable slurry.[33] The slurry was cooled to −15 to −10 °C, aged for a period of time and then filtered. The product was isolated as a light tan solid in a purity of 98.7%. The only impurity in the solid was the above-mentioned isomer. Compound **2f** was assigned the *E*-configuration shown in Scheme 1 on the basis that NOE experiments did not provide any interaction that was definitive of the stereochemistry about the double bond. There was a small NOE interaction between the olefinic β proton and the cyclohexyl H1 proton, but no positive proof of configuration.

Process Safety

Thermal testing of the concentrate taken during the solvent exchange from toluene to heptane showed a significant exotherm starting at 135 °C (TSU testing) (see Figure 1). The maximum changes in temperature and pressure for this exotherm were 31 °C/min and 27 bar/min, respectively. Ramping the batch temperature to 80 °C and holding for another 18 h also did not reveal any exotherm, although there was a slight increase in pressure.

In light of the potential for catastrophic thermal runaway with compound **2f**, advanced adiabatic thermal calorimetry and analysis were warranted (1) to ensure complete thermal energy accounting, (2) to extract the necessary quantitative data for scale-up to a full-scale reactor, and (3) to more accurately estimate the temperature onset sensitivity of explosion. Although temperature onset is a rather tenuous parameter being a function of the test apparatus used, the manner in which the test is conducted, the solvent boiling point, the reactor, ancillary equipment, and various ambient nuances under which the final chemistry is conducted (that is, it is the point at which the rate of thermal energy generated just exceeds the rate of energy loss) it is nonetheless an indispensible parameter for pragmatic implementation of large-scale chemistry. In our experience, adiabatic testing in the ARC, APTAC, or ARSST renders a reasonably conservative estimate of onset temperature for chemistries conducted in our particular pilot-plant reactors, unlike the TSU which is not, in general, operating in an adiabatic mode, consequently rendering it impossible to computationally remove the large thermal inertia influencing onset estimates.

APTAC test data, collected with the APTAC operating in ARC mode on another sample of the concentrate revealed, after computationally removing the thermal inertia of the test apparatus, a temperature onset of 77.7 °C (Figure 2). An abrupt acceleration in rate of temperature rise from 0.03 °C/min (at 77.7 °C) to 664 °C/min (at 183 °C) immediately followed; however, the pressure did not start to rise significantly until 130 °C.[34]

For the planned scale of operation and the reactor system selected, computations using an in-house developed spreadsheet

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(31) Since this was a site-specific requirement, lab-scale conditions for the conversion of **1** to **2f** in methylene chloride and isolation from heptane have been included in the Experimental section of this manuscript.

(32) Screening to assess the thermal hazards of the process was performed on the starting material, reaction mixtures, process concentrates, and the isolated solid. A variety of techniques were used for the screening including use of HEL's thermal screening unit (TSU), A. D. Little's accelerated rate calorimeter (ARC), TIAX's automatic pressure tracking adiabatic calorimeter (APTAC), and Fauske and Associates' advanced reactive system screening tool (ARSST). A summary of the experimental techniques and findings may be found in the Supporting Information.

(33) Oiling out of the product was never observed during the pilot-plant batches.

(34) The normal boiling point of this mixture was computed via Cosmo-Therm to be 132 °C.

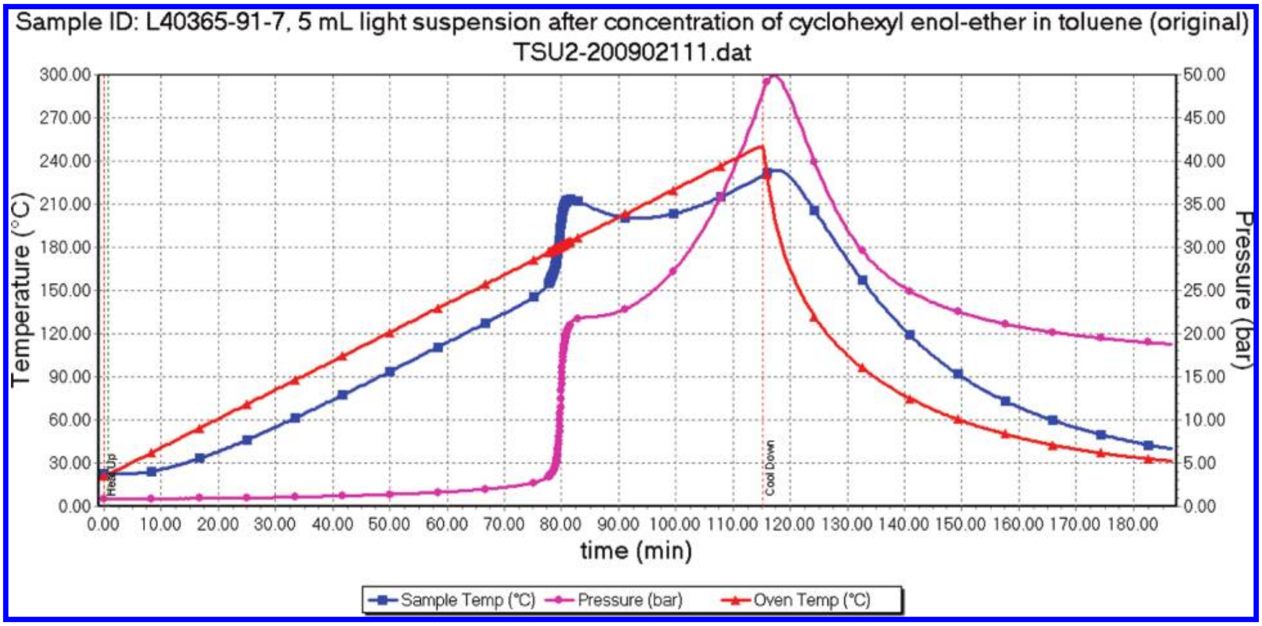

Figure 1. **TSU for concentrate of 2f in toluene.**

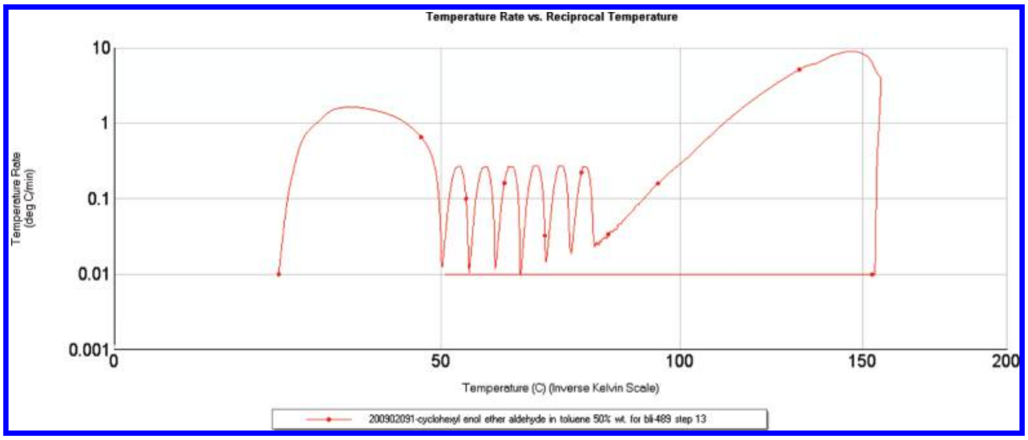

Figure 2. **APTAC test data (ARC mode) for concentrate of 2f in toluene.**

comprising DIERS[35] and derived equations (see Supporting Information) rendered a requirement for an emergency vent relief diameter of 7.4 in., a value that exceeded the 4.0-in. relief diameter available with the selected reactor system. With numerous parameters of a chemical process system impacting emergency vent relief capacity (e.g., solvent type, solvent quantity, reactant concentration, total mass, rupture disk burst set-pressure, vessel maximum working pressure, vessel volume, downstream relief piping) select parameters may be adjusted in order to fit a particular chemistry into a pre-existing relief diameter. In the present case, the solvent was preselected on the basis of product yield and process considerations, and the reactor system and scale on the basis of plant schedule and workup considerations. Therefore, the only remaining parameters for adjustment were the reactant concentration and solvent quantity. For a selected solvent quantity, the impact of the reactant concentration on required relief diameter is summarized in Figure 3.[36]

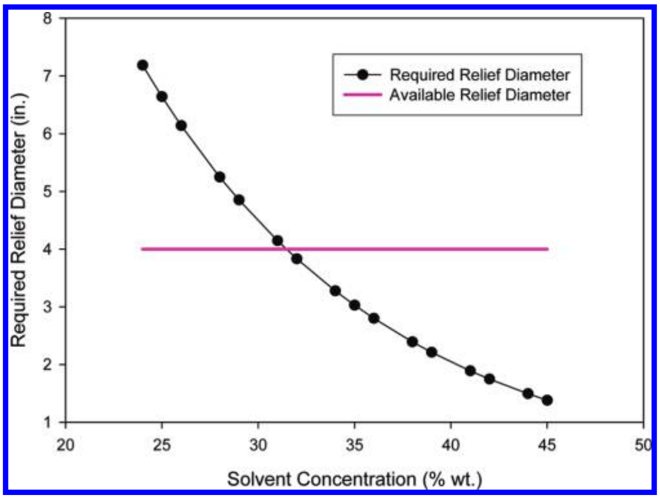

Figure 3. **Adjustment of solvent concentration to fit vent relief capacity.**

Figure 3 identifies a minimum solvent concentration restriction on operations of 31%. By specifying a minimum solvent concentration for the batch run, the effect on required emergency vent relief diameter had a two-fold, underlying cause. First, it ensured the presence of an adequate quantity of solvent acting as a heat-sink to absorb decomposition energy, thus limiting the temperature rise, the magnitude of the Arrhenius term, and in turn, the acceleration of the rate of heat generation. Also, it

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(35) Design Institute for Emergency Relief Systems.

imposes an upper limit to reactant concentration, which manifested itself via chemical kinetics as a second limit on the reaction rate. These combined limits on reaction rate, engendered by a restriction to a minimum solvent concentration, were sufficient to fit the chemistry into the chosen chemical reactor with a fixed, pre-existing 4-in. relief diameter. A minimum solvent concentration restriction of 34% was used and converted to a liquid level in the reactor for the operator not to fall below.[37]

In summary, thermal test data, information about the process equipment to be used, and the unit operations to be performed were integrated into heat balance, mass balance, and vent relief equations. These were then solved to identify where process upsets would occur, establishing boundaries of safe operation in terms of two critical processing parameters (namely, temperature control below approximately 77.7 °C and solvent concentrations above 31%). The minimum safe solvent concentration was controlled by maintaining a minimum liquid level in the reactor. Temperature was kept below 77.7 °C by conducting the concentration step under vacuum; maximum temperature attained during the run under vacuum was 33.9 °C.[38] Although it was anticipated that there would be sufficient evaporative cooling under vacuum to prevent the abrupt temperature and pressure rises witnessed in the APTAC, if vacuum were to be inadvertently lost, the proximity of the reflux temperature to the onset estimate was too close to risk. Hence, adequate emergency vent relief had to be invoked as a protective measure to compensate for the risk of a runaway.

Scale-Up

The process was scaled up from the 180-g laboratory run to 170−270 kg in a pilot plant. Processing proceeded smoothly; however, the solvent exchange from toluene to heptane required a significant amount of heptane to achieve the in-process specification for toluene content. On the largest executed scale, approximately 10,000 L of heptane was required in order to reduce the toluene down to within the acceptable range. One experiment was performed in the laboratory in which heptane was replaced with octane. Using the higher-boiling hydrocarbon reduced the solvent required for the exchange to approximately 25% of the total heptane charge and also led to shorter cycle times, given that less time was required for the distillation. However, project commitments drove our delivery and replacement of heptane with a higher-boiling hydrocarbon solvent was not persued.[39] A summary of the pilot-plant campaign is shown in Table 4.

Table 4. **Summary of the pilot-plant campaign**

batch size/purity (kg **1**/wt%)	final toluene/heptane IPC (GC A%)	product mass (kg **2f**)	product yield (%)	product purity (wt %)
269/97.3	4	331	79	96.6
169/93.7	4	202	80	97.1
258/96.8	4	320	81	97.1
170/97.6	2	221	85	98.6

The pilot-plant batches ran smoothly, especially in light of the scale-up factor. Lack of turbidity in the azeotropic distillate provided a visual indication of the end point for the reaction after which point, in-processing sampling was performed. Solvent exchange from toluene to heptane proved variable in the amount of heptane and time required, but good control of the toluene/heptane ratio end point was obtained that resulted in reproducible yield and purity. The filtration, washing, and drying operations were all performed without any issues or problems. In some cases, lab samples of **2f** that had been stored in polyethylene bags appeared to become sticky with time, so that as a result, larger-scale quantities were stored in double polyethylene bags with a desiccant between the inner and outer bags.

Conclusion

We have described the preparation of a new enol ether derivative of bromomalonaldehyde. This cyclohexyl derivative offers the advantage of being an isolable solid and should find utility in the synthesis of imidazolecarboxaldehydes. We have described a convenient laboratory-scale process that can be run at atmospheric pressure in methylene chloride and another process that can be run under partial vacuum in toluene. In both cases, product **2f** is easily isolated following an *in vacuo* solvent exchange to heptane. Extensive process safety testing of the later process established that the reaction mixture should not exceed 35 °C during the solvent exchange from toluene to heptane and demonstrated that the maximum concentration during the solvent exchange is quite dependent on the diameter of the relief vent available. The toluene/heptane process was scaled up to produce 1.1 MT of the product, and options for decreasing the anti-solvent usage have been described.

Experimental Section

General. Bromomalonaldehyde was prepared from tetramethoxypropane.[40] Cyclohexanol was purchased from Honeywell. Reaction monitoring was carried out on Waters Alliance HPLC with PDA monitoring (260 nm) equipped with a Sunfire C18 column (3.5 μm, 4.6 mm × 150 mm) at 35 °C. Elution was performed with a flow rate of 1.0 mL/min and a gradient

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(36) Ingredients to Figure 3 were kinetic data extracted from the APTAC run on a concentrated solution (50%); kinetic, mass, and energy balance equations found in Supporting Information as well as DIERS vent-sizing equations. Vent sizing assumed sonic, two-phase, tempered, homogeneous flow, and a burst pressure of 25 psig and accounted for the impact of emergency vent piping geometry on flow head losses.

(37) A retesting in the APTAC of a sample at 34% solvent was not conducted for confirmation of kinetic data, because this technique of extrapolating kinetic data based on concentration changes alone to a number of circumstances has been previously used and verified at Wyeth. However, because the activation energy is essentially a function of everything, it is generally prudent to retest, especially if changes in vessel material of construction, reagents, reagent lots, etc. are made.

(38) The distillation was run under a slightly better vacuum in order to lower the distillation below 35 °C and maintain an acceptable safety margin.

(39) Preliminary safety screening showed that there would be no additional thermal hazards if octane were used. Although the cost of octane was much higher than that of heptane, Isopar E, a mixture of high-boiling hydrocarbons with a boiling point of 118 °C, is available for ~$2.50/kg and appears attractive, although it was not evaluated as an antisolvent.

(40) Trofimenko, S. Dihalomalonaldehydes. J. Org. Chem. **1963**, *28*, 3243–3245.

method using 95% acetonitrile, 5% water, 0.05% TFA (mobile phase A), and 95% water, 5% acetonitrile, 0.05% TFA (mobile phase B) (Initial: 100% A, 50 min 100% B). Observed retention times were as follows: **1** (4.6 min), **2f-isomer** (26.0 min), **2f** (26.9 min).

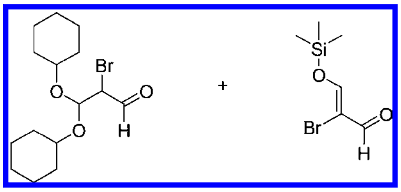
Caution. Compound **2f** contains a structural alert for being a α,β-unsaturated aldehyde when evaluated using Derek, an expert knowledge-based *in silico* predictor of chemical toxicity.[41] The starting material is also alerting for being a α,β-unsaturated aldehyde and an alkylating agent. Appropriate PPE should be used when handling these compounds.

TSU testing was performed in a thermal screening unit (HEL Ltd.). The samples were charged into a 9-mL test cell (Hastelloy C unless otherwise indicated), which was then sealed into an oven. The oven temperature was ramped up to 250 °C at 2 °C/min, unless otherwise indicated. Sample temperature was monitored with a thermocouple immersed into the sample. Sample pressure and oven temperature were also monitored throughout the run. The containment volume—test cell, pressure transducer and piping—was approximately 10 mL.

Lab-Scale Preparation of 2f in Toluene. A suspension of 2-bromomalonaldehyde 180 g, 1.2 mol), cyclohexanol (179 g, 1.8 mol, 1.5 equiv; contained 2.5 wt % water)[42] and *p*-toluenesulfonic acid in toluene (720 mL, 4 v/w equiv) was heated at 45−50 °C while under partial vacuum (120−80 Torr) and set up for distillation to remove water. Toluene was added as necessary over a 3-h period to maintain the reaction volume at the initial level. When in-process LC showed the reaction to be complete (**1**/**2f** < 1%), the vacuum distillation was continued, and the reaction mixture was reduced to 70−75% of the initial volume. Heptane was added in one portion to dilute the mixture to 130−150% of the initial volume, and solvent removal was continued. Heptane was added as required to maintain a constant pot volume. The resulting solution was cooled down to ~30−35 °C to initiate crystallization, then gradually cooled down to −15 to −10 °C and filtered using cold heptane (4 v/w, −5 to 0 °C) as a wash. The product was dried in nitrogen stream on filter to provide **2f** in 94% yield with HPLC purity 98% and strength 95%. ^{1}H NMR (300 MHz, d_6-DMSO): $\delta = 1.37, 1.56, 1.74, 1.98$ (four multiplets, 10H), 4.42 (m, 1H), 8.46 (s, 1H), 9.18 (s, 1H) ppm; ^{13}C NMR (400 MHz, d_6-DMSO): $\delta = 184.4, 168.9, 104.2, 84.0, 31.6, 24.5, 22.8$ ppm; HRMS for $C_9H_{13}BrO_2$: 232.0099 (calculated), 232.0115 (found), mp 66.5 °C.

Lab-Scale Preparation of 2f in Methylene Chloride. A suspension of 2-bromomalonaldehyde (50 g, 0.33 mol), cyclohexanol (50 g, 0.50 mol, 1.5 equiv) and *p*-toluenesulfonic acid (0.32 g, 1.7 mmol, 0.005 equiv) in methylene chloride (265 mL, 4 v/w equiv) was heated at 40−50 °C and set up for an atmospheric pressure distillation. Fresh methylene chloride was added as necessary to maintain a constant pot volume, while methylene chloride and water were removed. In total, 0.45 L of methylene chloride was added over a 3-h period. When in-process LC showed the reaction to be complete (**1**/**2f** < 1.5%), the distillation was continued under partial vacuum (down to 70 Torr) at 35−40 °C while adding heptane (total 10 v/w) to maintain a constant pot volume. A suspension had formed at the end of distillation that was cooled down to −15 to −10 °C, filtered, and washed using cold heptane (4 v/w, −5 to 0 °C). The product was dried on the filter with a nitrogen stream and afforded **2f** in a yield of 88% with a wt % purity of 95%.

Pilot-Plant-Scale Preparation of 2f in Toluene. 2-Bromomalonaldehyde (169 kg, 93.7 wt % pure, 1050 mol), *p*-toluene sulfonic acid monohydrate (1.06 kg, 99.4 wt % pure, 5.54 mols), toluene (591 kg) and cyclohexanol (172 kg, 99.8 wt % pure, 1720 mol, containing 0.1 wt % water) were charged to a 500-gal vessel equipped with a Dean−Stark separator. The mixture was heated under vacuum to reflux at a pot temperature of 20−35 °C (the pressure was about 40 Torr) until no further water was collected (26 h) while adding toluene (50 kg) portionwise; 19.7 kg of water was collected (cf. 19.2 kg theory). (**CAUTION**: ARC testing indicates potential runaway decomposition at temperatures as low as 78 °C if the concentration is 50 wt % or greater.) A sample of the batch was analyzed and found to contain 2.6% bromomalonaldehyde **1** (relative to **2f**) and 0.03 wt % water. Toluene solvent was replaced with heptane by distilling under vacuum to about 666 L, adding heptane (678 kg) and then continuing distillation while adding heptane to maintain the volume. The solvent replacement took 36 h and required another 3700 kg of heptane to achieve a ratio of toluene/heptane = 3.7% by GC. The batch was cooled −10 °C to induce crystallization and then filtered in three portions, washing each portion with 2 × 50 kg of chilled heptane. The product was dried under vacuum at 37 °C to obtain 202 kg of 97.1 wt % pure product (80% yield). The mother liquors were analyzed by GC/MS (with and without silation); in addition to **2f**, the main impurities were tentatively identified as shown below.



Acknowledgment

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Supporting Information Available

Selected process safety data for compound **2f** as well as the derivation of equations used to generate data to establish the relationship between concentration and the required relief vent diameter. This material is available free of charge via the Internet at http://pubs.acs.org.

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[41] Derek is commercially available from Lhasa Limited.

[42] The vendor provided cyclohexanol with water added to suppress the melting point. The melting point of cyclohexanol is 25 °C.