Supporting Information

A Scalable Synthesis of 2-(1,2,4-Oxadiazol-3-yl)propan-2-amine Hydrobromide using a Process Safety-Driven Protecting Group Strategy

Nachiket Likhite,[a] *Thirumalai Lakshminarasimhan,*[a] *Mallem H. V. Ramana Rao,*[a] *Vijaykumar Shekarappa,*[a] *Somprabha Sidar,*[a] *Varadharajan Subramanian,*[a] *Kenneth J. Fraunhoffer,*[b] *Simon Leung,*[b] *and Rajappa Vaidyanathan*[a]*

[a] Chemical and Synthetic Development, Biocon Bristol-Myers Squibb Research and Development Center, Biocon Park, Jigani Link Road, Bommasandra IV, Bangalore-560099, India

[b]Chemical and Synthetic Development, Bristol-Myers Squibb, 1 Squibb Drive, New Brunswick, New Jersey 08903, USA

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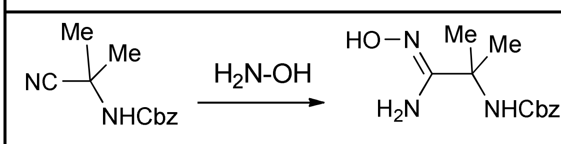
DynoChem® studies.

In the RC1e experiment, 10.6 g (1.4 equiv) of 50% aqueous hydroxylamine (dosing rate: 1.5 mL/min) was added to **2c** (25 g; 114.6 mmol) in 2-propanol (120 mL) at 55 °C. We realized that the heat data from reaction calorimeter obtained at two different temperatures could be used to fit the kinetics in DynoChem® software to find the optimum dosing time and reaction temperature. Thus in a separate experiment in RC1e, the hydroxylamine solution was added at faster rate (10.5 mL/min) at 35 °C and the heat data was recorded over a period 15-16 h. The heat data obtained from experiments done at two different temperatures was exported to the DynoChem® software for fitting the kinetics. In this case, the heat evolution rate (q_r) data corrected for baseline heat signal (q_r-q_b) was used for fitting the rate parameters.

Initially the rate constant, k at reference temperature (T_{ref}) was fitted for the heat data obtained at near isothermal reaction temperature of 35 °C and then the activation energy (E_a) was fitted for the other run carried out at 55 °C. As seen from the Figures S1 and S2, a good fit of experimental and predicted heat data was obtained and the reaction was determined to be first order in **2c** and hydroxylamine as initially assumed in the model (Table S1)

Table S1. Rate equations used for kinetic fitting in DynoChem® Software

Reaction	**T_{ref}**	**Order**
 **2c** **3c**	35 °C	First order in **2c** and hydroxylamine

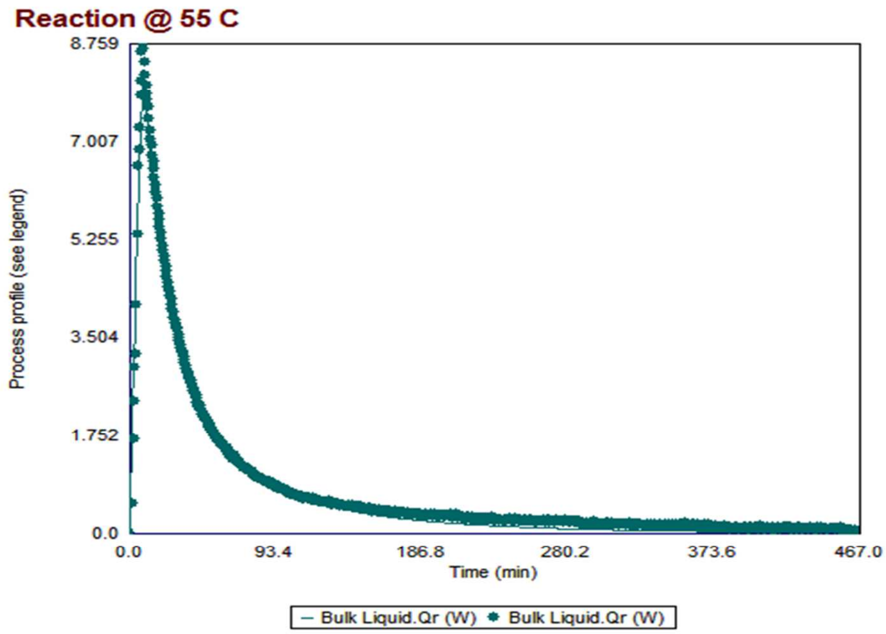


Figure S1. Fitting of q_r data for the RC1e run done at 55 °C

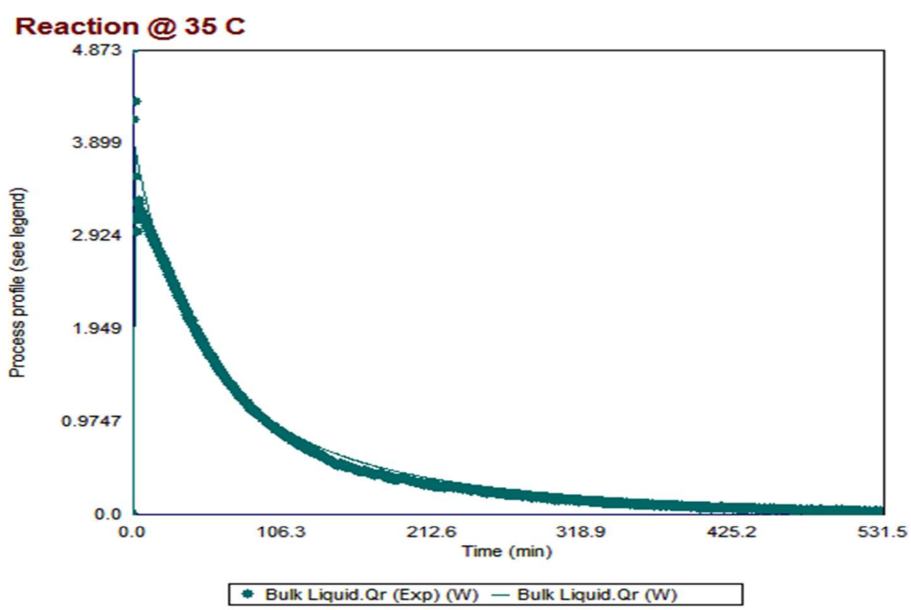


Figure S2. Fitting of q_r data for the RC1e run done at 35 °C

As seen from Table S2, the formation of **3c** is not very sensitive to temperature (E_a = 38.3 kJ/mol).

Table S2. Fitted kinetic parameters from DynoChem®

Parameter	value	confidence intervals (%)	Unit
k	1.96×10^{-4}	± 1.5	L/mol.s
E_a	38.3	$\pm$ 1.8	kJ/mol
ΔH_r	−175.05	± 0.8	kJ/mol

Maximum accumulation is a function of both the reaction temperature and dosing time, which requires two dimensional optimization. A response surface plot of dosing time, reaction temperature and Maximum Heat Accumulation was generated using the feed time and the temperature as a variable in the model.[1] Temperature was used as a variable to calculate the reaction temperature based on the cooling capacity of the reactor which is a function of the overall heat transfer (UA) and the temperature difference [ΔT, where ΔT = reaction temperature (T_r) - jacket temperature (T_j)], as shown in Eq.1. The temperature profile in the reactor is obtained by integrating Eq.1. A simple controller was also used in the model to calculate the T_j based on the deviation from the set temperature (T_{set}) and the proportional gain (K_P) as shown in Eq.2. This was more realistic, as a variation of T_r may have an impact on the required feed time.

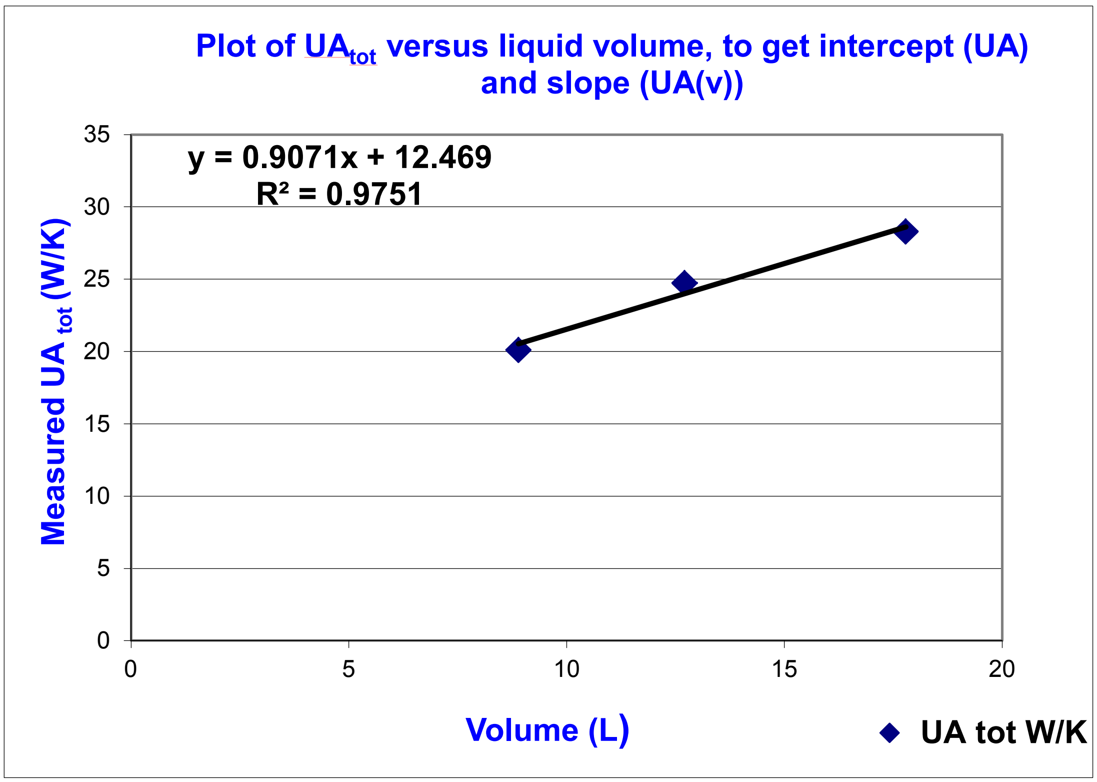
$$\frac{dT}{dt} = \frac{q_r}{mC_p} - \frac{UA}{mC_p}\Delta T \qquad \text{Eq. 1}$$

$$T_j = T_{set} - K_p * (T_r - T_{set}) \qquad \text{Eq. 2}$$

As shown in Figure S3, the variation of UA with liquid volume (V) was incorporated in the model (Eq 3) by doing solvent tests in a 30 L glass reactor.

$$UA_{tot} = UA + UA(V) * Volume \qquad \text{Eq. 3}$$

Figure S3. Variation of UA with volume for a 30 L glass reactor



A two dimensional surface plot was generated in DynoChem®, by varying the feed time from 30 to 600 min in 21 levels and the temperature from 50 to 80 °C in two steps (16 levels). In all 336 (21* 16) scenarios were generated and used for generating the plot in Excel.

Impact and Friction sensitivity tests

BAM falling hammer impact sensitivity test was conducted with a Type MP-3 Falling Hammer from the Swiss Institute for Promotion of Safety and Security following a published procedure.[2] Negative results were observed in six trials at impact energy of 60 J. As a result, the material is not considered to be impact sensitive.

BAM friction sensitivity test was conducted with a HAAKE model 002-5792-9300 friction tester following a published procedure.[3] Negative results were observed in six trials at a friction force of 360 N. As a result, the material is not considered to be friction sensitive.

References:

(1) Applications of DynoChem in Thermal Process Safety – Optimization of Accumulation and Time to Maximum Rate by Bernhard Berger can be found at https://dcresources.scale-up.com

(2) UN Transport of Dangerous Goods: Classification Procedures, Test Methods and Criteria Relating to Explosives of Class 1, section 13.4.2

(3) UN Transport of Dangerous Goods: Classification Procedures, Test Methods and Criteria Relating to Explosives of Class 1, section 13.5.1