

Lab Automation in Support of Safer Process Design for HWE Reaction

S. E. Gottschling, P. Krasik, and D. Levin*

NPIL Pharma Torcan, Aurora, Ontario, Canada LAG 3H4

Abstract:

A scaleable process technology has been developed for a Horner–Wadsworth–Emmons reaction. The basic calorimetry capability of the MultiMax automated reactor system afforded some interesting insights regarding scale-up safety of the original process and helped guide us to improve alternative chemistry more suitable for safe scale-up.

Introduction

Torcan's business is in pharmaceuticals contract research, development, and manufacture. A recent project required us to develop scaleable process technology for a Horner–Wadsworth–Emmons (HWE) reaction.¹ The original procedure received for this reaction step (Scheme 1 and Appendix 1) comprised controlled addition of (wax coated) sodium hydride powder to a phosphonate in THF at 0 °C, followed by stirring at 0 °C for 30 min, slow addition of an aldehyde at 0 °C, heating to 45 °C and stirring at 45 °C before workup.

Due to concerns about potential process operational hazards on scale-up (associated with risk of air ingress to a flammable solvent vapour in the reactor on addition of sodium hydride powder), in addition to the difficulties in achieving controlled addition of a reagent in powder form, plus comments in the original procedure regarding poor reaction rate control, work was done to compare the current reaction conditions against a screen of alternative bases using our Mettler Toledo MultiMax ART automated reactor system.² As a result of this work, the basic calorimetry capability of the MultiMax afforded some interesting insights regarding the progression and the scale-up safety of the original procedure and helped guide definition of improved alternative chemistry more suitable for safe scale-up.

Results and Discussion

On running the original reaction procedure in the MultiMax equipment using 50-mL jacketed reaction vessels with overhead stirring, it became apparent from comparison of the batch temperature profile inside the reactor (**Tr**) compared with the reactor jacket temperature profile (**Tj**) that little or no reaction was actually taking place during controlled addition of sodium hydride powder at 0 °C or after the addition and stirring with the aldehyde at 0 °C. It was only after heating the mixture of phosphonate, aldehyde, and

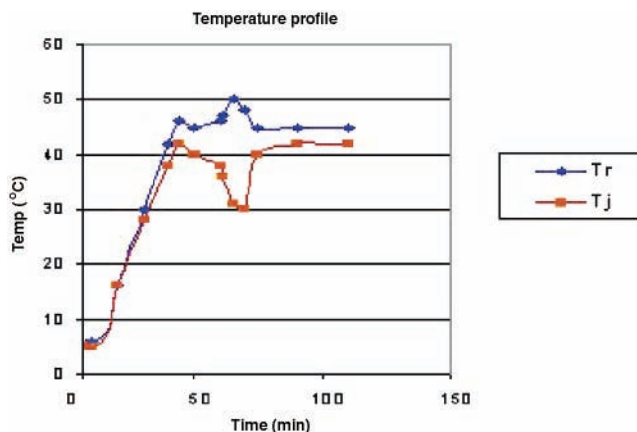


Figure 1.

sodium hydride slurry in THF to 45 °C that a significant exotherm occurred, as evidenced by the significant deviation between **Tr** and **Tj** (Figure 1), whilst the MultiMax struggled to maintain the reaction temperature setpoint of 45 °C by increasing chilling of the reactor jacket fluid to compensate for the heat generated in the reaction mixture. Although at 50-mL scale the MultiMax was eventually able to accommodate the reaction exotherm by means of a 15 °C reduction in the jacket temperature, thanks to the relatively high surface area-to-volume ratio available at that scale, this would translate to a significant process safety problem on scale-up. This is because the consequence of increasing the reaction scale from 50 mL to 1000 L production equipment would result in an approximately 50-fold deterioration in surface area-to-volume ratio, with consequent penalty to both heat transfer efficiency as well as the efficiency of disengaging the hydrogen gas (byproduct of deprotonation) from the reaction mixture.

The heat generated during an exothermic chemical reaction is proportional to the batch size (number of moles present in the reaction), which (assuming efficient use of vessel capacity) is in turn dictated by the vessel volume, $\propto r^3$ (the cube of the vessel radius) as the batch size varies; however, the ability to remove heat is limited by the surface area of the jacket in contact with the reaction mixture which varies with reaction scale $\propto r^2$. Thus, as scale increases, heat generation $\propto r^3$ increases faster than the ability to remove that heat $\propto r^2$ so that the temperature of the reaction mixture increases. The consequence of higher reaction temperature is that the reaction rate also increases according to the Arrhenius equation:³

$$k = A \exp\left(\frac{-E_a}{RT}\right)$$

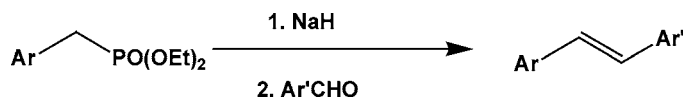
(3) http://en.wikipedia.org/wiki/Arrhenius_equation.

* Author to whom correspondence should be addressed. E-mail: danny.levin@torcan.com.

(1) <http://www.organic-chemistry.org/namedreactions/wittig-horner-reaction.shtm>.

(2) <http://glo.mt.com/home>.

Scheme 1



where k is the rate coefficient, A is a constant, E_a is the activation energy, R is the universal gas constant, and T is the temperature (in kelvins).

The faster reaction rate with increasing temperature then results in yet faster heat generation, and with heat transfer ability still compromised compared with that in smaller laboratory-scale equipment, the consequence can be a dangerous thermal runaway where reaction rate and heat generation increase out of control, with rapid vaporisation of reaction solvent, rapid pressurization of reaction vessel, and potentially an explosion if the rate of pressure buildup exceeds the rate at which the gas pressure can be vented.⁵

A similar situation applies regarding disengagement of the hydrogen gas evolved from reaction of sodium hydride with the phosphonate. The ability to disengage this gas from the reaction mixture is dictated by the volume of gas evolved divided by the area of the top surface of the reaction mixture through which the hydrogen gas has to bubble to escape. As scale increases, the efficiency of gas disengagement deteriorates such that the reaction mixture is increasingly likely to froth up as a foam, with consequent risk of pressurization and/or loss of toxic, flammable, and reactive reaction mixture through reactor vents.

It is therefore important to ensure that the rates of both heat and gas generation are strictly controlled throughout the course of the reaction to ensure safety on scaleup. This is best achieved for rapid, highly exothermic reactions by ensuring that reactions are controlled by the rate of addition of one of the key reagents, without accumulation of unreacted reagent during the addition, such that there is no reservoir of unreacted reagent present that is capable of reacting all at once. In the case of the original HWE reaction procedure described above, the MultiMax temperature traces showed that, despite slow addition of sodium hydride and aldehyde, there was, in fact, significant or even complete accumulation of unreacted sodium hydride and aldehyde through the course of these additions at 0 to 5 °C, presumably due to the heterogeneity of the reaction mixture resulting in very slow reaction of the insoluble sodium hydride base with the phosphonate solution. It was only after the temperature was then raised to 45 °C that a significant reaction rate ensued, but by then the entire reaction quantity of sodium hydride, phosphonate, and aldehyde had been added so that once reaction ensued there was no further recourse to limit the extent of the reaction or the reaction exotherm by controlling the addition of one or other reagent. An alternative expedient could have been to explore controlled addition of one of the key reagents at the temperature at which the reaction did proceed (i.e. at around 45 °C); however, the heterogeneity and operational difficulties associated with sodium hydride

prompted evaluation of alternatives. The MultiMax was accordingly used to screen different bases for the reaction with the objectives of achieving control of the reaction by rate of reagent addition and ideally avoiding the complications associated with solid reagent addition to a flammable reaction mixture. Sodium hexamethyldisilazide (NaHMDS) solution in THF⁴ was accordingly shown to be an ideal alternative to sodium hydride, and a safe, scaleable reaction procedure was developed that was based on use of this reagent whereby the NaHMDS solution was added in a controlled fashion to the phosphonate in THF at -20 °C. The resulting phosphonate anion solution was heated to 20 °C, and the aldehyde component (which is a liquid) was added in multiple portions at 20 °C to give the product in high yield and with good control of the heat of reaction, commensurate with reagent addition, at all steps of the process. It was furthermore confirmed that, although 11% of the unwanted *cis* geometrical isomer was formed by the HWE reaction, the stereochemical outcome of this step was of no consequence for downstream API as the *cis:trans* mixture generated during the HWE step was improved during crystallization isolation and was furthermore fully isomerised to the *trans* isomer during downstream processing. The NaHMDS-based chemistry was accordingly successfully scaled up to deliver safe and efficient manufacture to meet our client's needs.

Conclusions

Scale-up safety issues arising from reagent accumulation during HWE reaction using solid sodium hydride as base were anticipated with the aid of the MultiMax automated reaction system, and a safely scaleable alternative was defined as a result, employing controlled addition of NaHMDS solution at -20 °C, followed by portionwise addition of aldehyde at 20 °C, under which conditions no reagent accumulation occurred and the heat of reaction was completely controlled by rate of reagent addition at the two exothermic steps (of base addition and aldehyde addition).

Appendix 1: Original Procedure Received for the HWE Reaction (Scheme 1)

To a solution of the phosphonate (0.6 kg) in THF (3 L) at 0 °C was added sodium hydride (0.17 kg, 60–65% in wax) under nitrogen. After the addition was completed, the suspension was stirred at 0 °C for 30 min and the aldehyde (0.19 L) was added over approximately 3 h. The reaction was then heated gradually to 45 °C and maintained at that temperature for 6–8 h (monitored by TLC). (Note: During the heating process the reaction was prone to proceed quite vigorously, starting at any temperature. When this occurred, the heating would be temporarily discontinued until the reaction had slowed down in the interests of safety and the reaction would then be completed with slower temperature

(4) http://www.basf.com/inorganics/pdfs/tech_datasheet/NaHMDS.pdf.

(5) Compare Bretherick's *Handbook of Reactive Chemical Hazards*, 6th ed.; Compiled by Pitt, M. J.; Urben, P. G., Ed.; Butterworth-Heinemann: UK, 1999; Vol. 1, page xxii.

ramp.) The reaction was cooled to 0 °C. Cold (ice) water (250 mL) was added slowly to quench the reaction. The mixture was then extracted with ethyl acetate (two to three times, each time 3 L). The combined extracts were washed with water (2 × 2 L) and saturated brine (2 × 2 L) and were dried (Na₂SO₄). Solvent was removed by evaporation

to give crude product which was then recrystallised from methanol (12 to 15 L) to give the pure product in 61% yield.

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