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In Situ FTIR Study and Scale-Up of An Enolization−Azidation Sequence†

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Abstract:

A key step in the synthesis of an optically active aminoalcohol-containing active pharmaceutical ingredient (API) involved the diastereoselective introduction of an azido functional group on a functionalized chiral oxazolidinone. This was accomplished via a low-temperature enolization, followed by a quench with triisopropylbenzenesulfonyl azide. To enable scale-up of this process, the enolization temperature had to be increased from the original <−65 °C to approximately −40 °C. *In situ* FTIR was used to study the enolization and quench stages of the reaction. The half-life of the enolate at −45 °C was estimated to be 12 h on the basis of *in situ* FTIR profiling. Examination of the *in situ* FTIR data also provided evidence that the reaction between the enolate and triisopropylbenzenesulfonyl azide was instantaneous and demonstrated that accumulation of triisopropylbenzenesulfonyl azide did not occur. A combination of *in situ* FTIR experiments and traditional parameter ranging experiments resulted in a process that was successfully run at −40 °C without an appreciable erosion of facial selectivity or yield.

Introduction

The evolution of a synthetic process from initial discovery synthesis to the successful preparation of multikilogram quantities of compound **1** has been communicated previously.[1] Installation of the chiral center bearing the nitrogen relied on methodology developed by Evans[2] that involved low-temperature enolization of oxazolidinone derivative **2** followed by conversion to azido intermediate **5** with triisopropylbenzenesulfonyl azide (trisyl azide) and reduction (Scheme 1).[3]

The original Discovery conditions involved performing the enolization and trisyl azide addition sequence below −65 °C. Although these conditions were suitable for the first Chemical Development batch of **1**, these low-temperature conditions could not be achieved in our 50-L Hastelloy vessel. In order to allow for heat of mixing and a slight exotherm for the reactions, the kilolab team recommended that the process be evaluated in the laboratory at an internal reaction temperature of ∼−40 °C. Further processing constraints were added by Wyeth's Chemical Development Material Operations Group, who informed the team that trisyl azide was more easily and economically sourced as a 30 wt % solution in toluene than as an isolable solid.

Results and Discussion

The process initially used by Chemical Development involved addition of 1 equiv of 0.5 M potassium hexamethyldisilazane (KHMDS) in toluene to a solution of **2** in 6.5 volumes of THF, while the internal batch temperature was maintained below −65 °C, followed by a solution of trisyl azide in 4 volumes of THF, then acetic acid and finally water. The high dilution of substrate and base had a detrimental impact on throughput in the 50-L vessel. The maximum batch size that could be processed was approximately 2.8 kg of **2**, based on V_{max} being below 48 L following the acetic acid addition.

Significant improvements were made with respect to throughput by reducing the amount of solvent to dissolve **2** from 6.5 to 2.5 volume equivalents, which still kept **2** completely in solution even at the low temperatures required for the process, and by the use of more concentrated 0.91 M KHMDS in THF. These two changes along with use of a 30 wt % solution of trisyl azide in toluene allowed the batch size to be increased to 5 kg of **2** based on a V_{max} of 48 L.

With process throughput improved, efforts were then focused on increasing the operating temperature to the −40 to −50 °C range requested by the kilogram laboratory team. A series of experiments were performed that addressed the operating temperature and robustness of the process by extension of addition times and evaluation of a series of hold times. The results of this study are shown in Table 1.

This study indicated that increasing the enolization operating temperature did not have a significant detrimental impact on the conversion of **2** to **5** within the processing times examined, suggesting higher temperatures were acceptable. During this work, an intermediate assumed to be **4** was observed by LC.[4] Intermediate **4** did not decompose to **5** until acetic acid was added.

To gain insight into the kinetics of the reaction and to further evaluate the stability of intermediates (in parallel with the parameter ranging experiments reported above) *in situ* FTIR was evaluated as a process analytical technology (PAT) method. Several recent reports have highlighted the utility of using PAT to gain better process understanding, and *in situ* FTIR has been established as an important tool.[5−8]

We established that the wavelength region between approximately 2200 and 1550 cm^{-1} contained no interfering peaks from the solvent (THF) and the starting material **2** had a strong stretching band at 1825−1775 cm^{-1} due to the oxazolidinone carbonyl group (Figure 1). As KHMDS (0.91 M in THF) was

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(3) Safety screening performed in-house generated results in line with those reported previously by Merck workers for triisopropylbenzenesulfonyl azide. See: Tuma, L. D. *Thermochim. Acta* **1994**, *243*, 161–167. A review of the thermal behavior of several sulfonyl azides is available: Bollinger, F. W.; Tuma, L. D. *Synlett* **1996**, 407−413.

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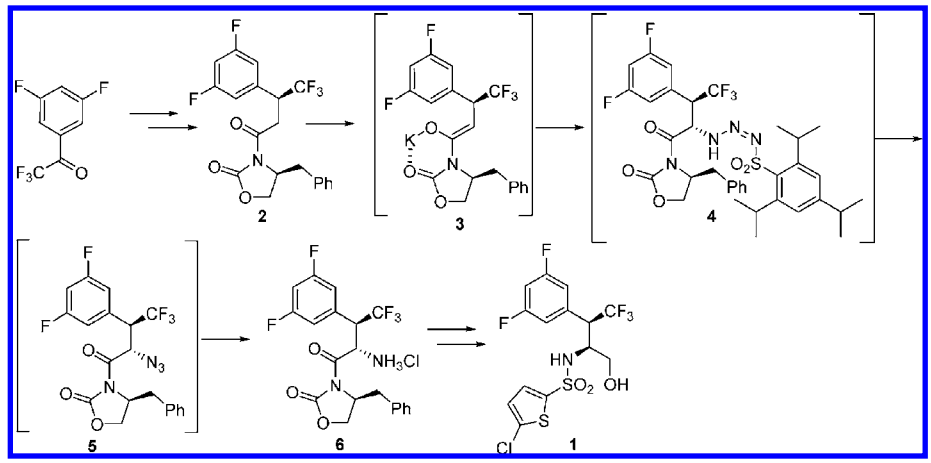
Scheme 1. **Synthesis of 1**



added to **2**, the peak representing **2** disappeared, and a new peak for the enolate **3** grew in at 1740−1715 cm^{-1}.[9] After a 30 min hold time, a solution of trisyl azide in THF was added and led to the disappearance of the peak for **3** and reappearance of the carbonyl band at 1825−1775 cm^{-1}.[10] It was interesting to note that, although trisyl azide had a very strong stretching band at 2125 cm^{-1}, no adsorption at this frequency was observed during the addition of trisyl azide.[11] This indicated that the reaction between the enolate **3** and trisyl azide to form **4** was fast enough at this temperature to prevent any accumulation of trisyl azide. It was only at the end of the reaction that a small increase occurred at 2150−2090 cm^{-1} due to a slight overcharge of trisyl azide. A timecourse plot of the peaks of interest is shown in Figure 2.

If the enolate was held at −45 °C for 4 h before the solution of trisyl azide was added, the enolate signal decreased by

Table 1. **Summary of parameter ranging experiments**

entry	temperature (°C)	base addition time (min)	enolate hold time (min)	temperature of trisyl azide solution (°C)	hold time after trisyl azide addition (min)	assay yield (%)[a]
1	−78	30	45	−78	2	90
2	−50	10	45	−78	2	87
3	−30	10	40	−78	2	86
4	−78	2	30	−78	60	97
5	−40	10	45	−78	2	92
6	−40	30	40	25	75[b]	98
7	−10	5	30	25	15	94

[a] Determined using HPLC. [b] Trisyl azide was added over 75 min in this example.

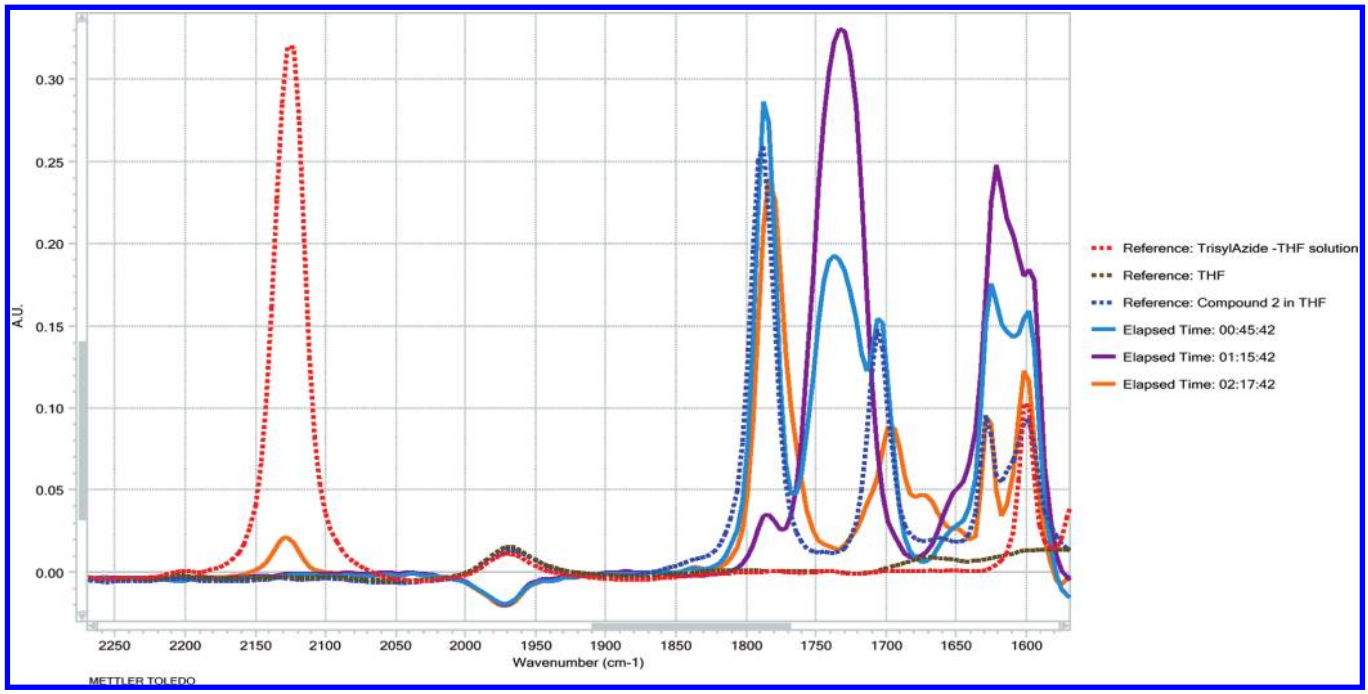


Figure 1. **IR spectral region of interest.**

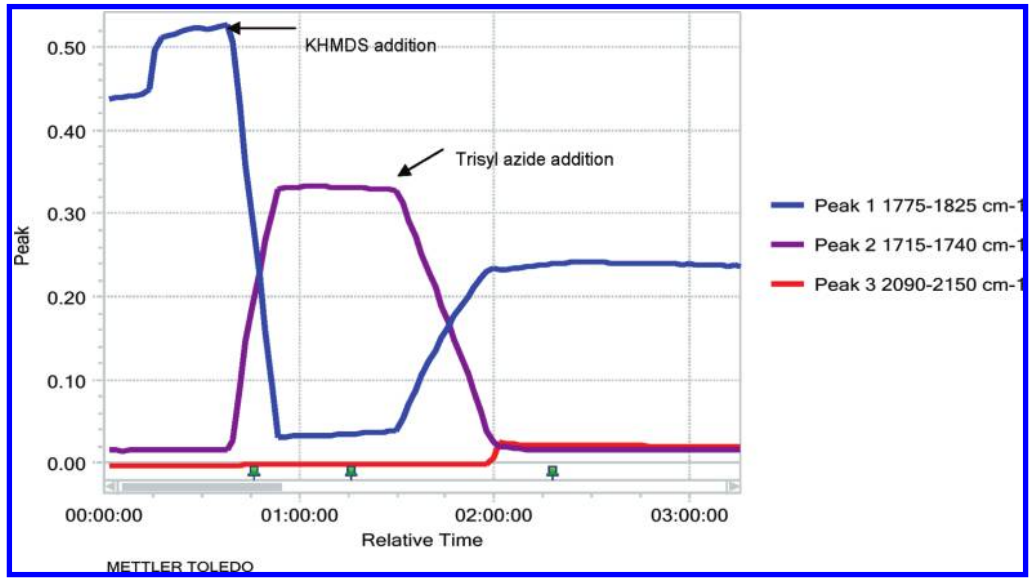


***Figure 2. In situ* FTIR profile at −45 °C for KHMDS and trisyl azide additions.**

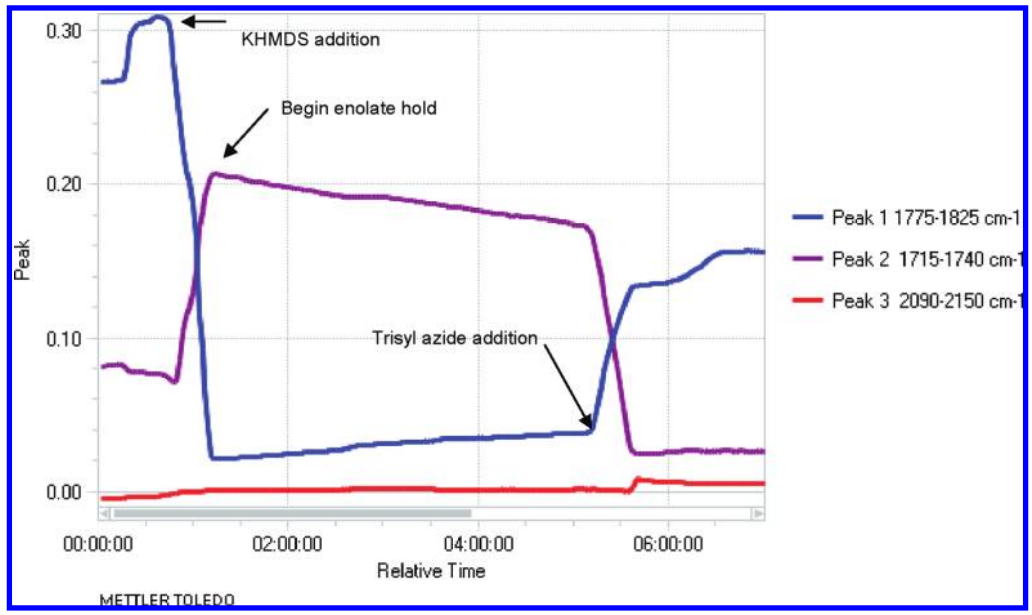


***Figure 3. In situ* FTIR profile at −45 °C for KHMDS and trisylazide additions.**

approximately 16% (Figure 3).[12] Extrapolation assuming linear decay provided an estimate of approximately 12 h for the half-life of the enolate at −45 °C. Performing the enolization at −10 °C and holding the solution overnight led to complete decomposition of the enolate and suggested a half-life of 2.5−3 h (Figure 4). In this case, addition of trisyl azide after the overnight hold led to an immediate appearance of the azide stretch since none of the reagent was consumed.

These *in situ* FTIR experiments provided some insight into enolate stability and led us to scale up entry 6 in Table 1 to 3 L. Although the experiment summarized as entry 7 in Table 1 gave excellent results on a small scale, the potential liabilities of the 3 h half-life of enolate **3** at −10 °C were viewed as being too large. Scale-up to approximately 100 g of **2** afforded a 93% assay yield of **5**. Aqueous acetic acid was added, and the

(4) The Evans group has isolated this type of intermediate and determined that it exists as a mixture of two tautomers. We have only shown one form here. For further details on the structural assignment of a sulfonylated triazine as an intermediate, see ref 2.

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(8) Rein, A. J.; Donahue, S. M.; Pavlosky, M. A. *Curr. Opin. Drug Discovery Dev.* **2000**, *3*, 734–742.

(9) This peak also corresponds to the oxazolidinone carbonyl group. Enolization to **3** is expected to result in a lower stretching frequency for the carbonyl group. The stretching frequencies of the oxazolidinone carbonyl groups of *N*-acyl and *N*-methyl oxazolidinone occur at 1795 and 1735 cm^{-1}, respectively.

(10) In this case, THF was used for dilution of the azido transfer reagent to remove any interference from another solvent.

(11) This stretch was assigned as the asymmetric stretch due to the N_3 group on the basis of vapor phase data published recently by the Novartis group. See: Wiss, J.; Fleury, C.; Onken, U. *Org. Process Res. Dev.* **2006**, *10*, 349–353.

(12) The solution of **3** remained homogenous over the hold period so the decrease in signal strength was not due to precipitation of the enolate species.

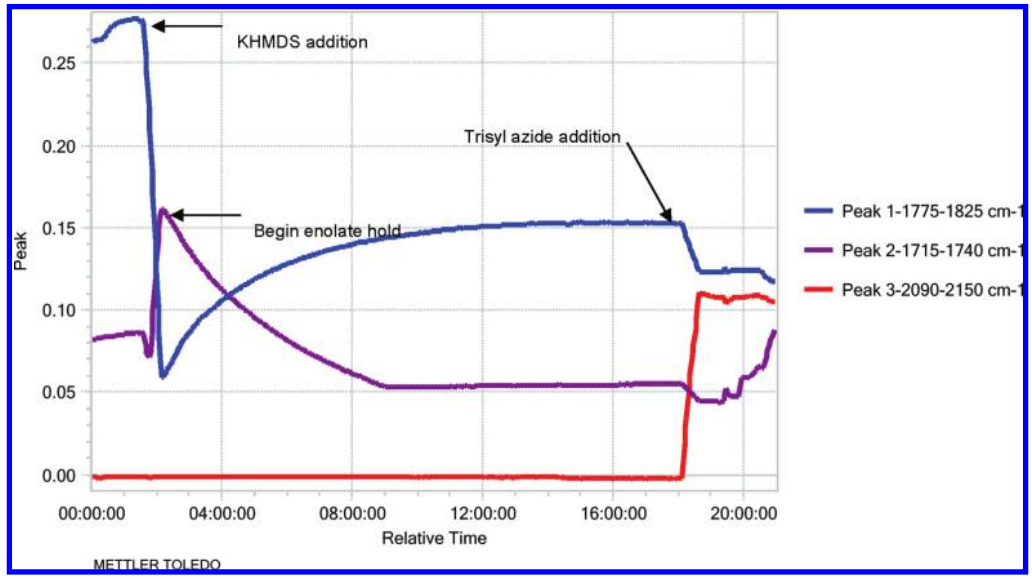

***Figure 4. In situ* FTIR profile at −10 °C for KHMDS and trisylazide additions.**

reaction mass was then warmed to ambient temperature to affect conversion of **4** to **5**.[13] Heptane was added and the organic layer washed with aqueous potassium phosphate to remove the sulfinic acid byproduct. The organic solution was exchanged under vacuum to ethanol, and the reduction to **6** was performed using conditions already reported.[1] The diastereomeric ratio of product **6** was comparable to results achieved when the enolization was performed at −65 °C, indicating that facial selectivity was not affected by performing the enolization at the higher temperature.

Conclusion

In situ FTIR studies were used in combination with traditional parameter ranging experiments in the development of an enolization−azidation sequence and to establish the temperature range for acceptable enolate stability.

Experimental Section

General. Reaction monitoring was carried out on an Agilent 1200 series HPLC with PDA monitoring (210 nm) equipped with an Agilent Extend C-18 column (3.5 mm × 100 mm) at 35 °C. Elution was performed with a flow rate of 1.0 mL/min and a gradient method using acetonitrile (mobile phase A) and water containing 0.1% H_3PO_4 (mobile phase B) (Initial: 50% A, 12 min 90% A, 15 min 90% A). Observed retention times were as follows: **6** (2.37 min), toluene (4.34 min), triisopropylbenzenesulfinic acid (4.76 min), **5** (8.34 min), **2** (7.17 min), trisyl azide (12.09 min).

In situ FTIR experiments were performed using a Mettler-Toledo ReactIR system (ReactIR4000 with K6 conduit and 16 mm SiComp probe). A SiComp probe was used because the area of interest to be examined extended above 2000 cm^{-1} (unsymmetrical azide stretching). IR spectra were recorded every 2 min at 8 cm^{-1} resolution, and spectral data were collected over the 4000−650 cm^{-1} range. Peak heights were measured from the zero baseline after a baseline offset was applied. Each *in situ* FTIR experiment was performed in a 25 mL three-neck round-bottom flask. Compound **2** (1.50 g) was dissolved in THF (8 mL) and cooled to the desired reaction temperature, which was measured using a thermocouple inserted into the reaction vessel. KHMDS (4.5 mL, 0.91 M in THF) was charged via syringe pump over 15 to 30 min. The mixture was held for the specified period of time at the reaction temperature, and trisyl azide (1.12 g in 3.5 mL THF) was added over 30 min, followed by HOAc, and the reaction mixture was warmed to ambient temperature.

Preparation of 5. A solution of THF (350 mL) and **2** (106.95 g at 93.5 wt %, 242 mmol) was maintained at −40 to −50 °C as KHMDS (266 g, 0.91 M in THF, 266.1 mmol) was added over 20 min. The resulting mixture was held between −40 and −50 °C for 25 min and a precooled (∼−65 °C) solution of trisyl azide (249.5 g, 30 wt % in toluene, 242 mmol) was added via cannula over 7 min as the temperature was maintained between −50 and −40 °C. The flask and cannula were rinsed forward with THF (30 mL), and the reaction mixture was stirred for 15 min at −45 °C. Acetic acid (66 g, 4.6 equiv) in water (70 mL) was added over 2 min, raising the temperature from −47 to −25 °C. The reaction mixture was warmed to ambient temperature and stirred until in-process HPLC indicated <1% of **4**. Assay of the resulting reaction mixture indicated clean conversion to **5** (approximately 101 g, 93%). Heptane (250 mL) was added to the mixture, and the organic layer was separated. The organic layer was washed with an aqueous solution of potassium phosphate tribasic (3 × 250 mL of 0.25 M solution) at 30 °C. The organic layer was concentrated to an oil.

(13) Addition of acetic acid as a neat liquid caused some stirring problems that were eliminated by adding the acetic acid as an aqueous solution.

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