Organic Process Research & Development **2003**, *7*, 514–520

Chemical Development on the Chiral Auxiliary (*S*)-4-(Phenylmethyl)-2-oxazolidinone Utilizing Automated Synthesis and DoE

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Abstract:

Enantiopure 4-substituted oxazolidinones are well-known chiral auxiliaries for asymmetric synthesis of carboxylic acid derivatives. The 4-(phenylmethyl)-substituted oxazolidinones derived from D- or L-phenylalanine are known to be particularly useful. We have conducted chemical development studies toward an efficient and scaleable "one-pot" process for production of (*S*)-4-(phenylmethyl)-2-oxazolidinone 2. The first step in the process employed a sodium borohydride reduction of phenylalanine mediated by an additive. The second step utilized triphosgene as a phosgene source to effect cyclization of the intermediate amino alcohol. Both chemical steps and workup procedures were screened and optimized utilizing statistical design of experiments (DoE) and parallel synthesis. The procedure was further characterized in an automated reactor system that provided heat flow measurements and modeled production at the plant scale. The efficiency of this process was compared to those of others previously reported on the basis of raw material cost, time requirements, safety, and hazardous waste generation.

Introduction

Enantiopure 4-substituted oxazolidinones are well-known chiral auxiliaries for asymmetric synthesis of carboxylic acid derivatives.[1] The 4-benzyl substituted oxazolidinones **2** derived from D- or L-phenylalanine have proven to be particularly useful. In addition to being crystalline solids, they provide high levels of asymmetric induction, and the acylation/hydrolysis steps are particularly facile. In connection with our program of supported reagent development, we sought an efficient and scaleable process for the production of **2**.

The initial synthesis of **2** reported by Evans employed BF_3-catalyzed borane−DMS reduction of phenylalanine (Phe) to afford the amino alcohol **1**. Following isolation, intermediate **1** was then cyclized using diethyl carbonate at 135 °C in the presence of base.[2] Although effective, the reduction step was reported to have dangerous induction periods resulting in violent eruptions on scale-up to the 0.5 mol level.[3] These safety issues were addressed by running the reaction at a higher temperature in DME and carefully controlling the rate of borane−DMS addition to minimize the build up of high-energy intermediates.[3] Throughout the 1990s, many additional syntheses of **2** were reported.[4] A survey of these showed that four of them could be amenable to scale-up. Following a critical analysis of these procedures, we centered our study on a sodium borohydride ($NaBH_4$) reduction of Phe, without the use BF_3−etherate, followed by cyclization of the intermediate amino alcohol **1** with a phosgene equivalent. Herein, we report the screening, optimization, and validation of a new one-pot process for the efficient and scaleable production of **2**.

Results and Discussion

Screening. The synthesis was broken out to the two individual steps for screening and optimization work (Scheme 1). For the reduction of Phe to amino alcohol **1** in THF (step 1), a series of three additives were examined. The function of the additive in this sodium borohydride reduction is to form diborane in situ.[5] The diborane, or the BH_3−THF complex, is the active reducing species. The additives studied included sulfuric acid,[5] chlorotrimethylsilane,[6] and iodine.[7] Reactions were conducted utilizing an Advantage Series 2050 manual chemistry synthesizer[8] (AS 2050) and the products were isolated by an extractive aqueous workup to determine the yield. The results are shown in Table 1.

The sulfuric acid procedure was repeated 4 times (entries 1−4) in order to assess its reproducibility. Uniformly high yields (91−95%) were obtained with products isolated as white waxy solids. The chlorotrimethylsilane (TMS−Cl) procedure was replicated 3 times and gave none of the desired product upon extraction of the reaction mixture. Presumably, the unreacted Phe remained in the aqueous layer. The iodine procedure was replicated twice and lead to isolation of product in excellent yield. The products from

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(7) (a) Freeguard, G. F.; Long, L. H. *Chem. Ind.* **1965**, 471. (b) Kanth, J. V. B.; Periasamy, M. *J. Org. Chem.* **1991**, *56*, 5964. (c) McKennon, M. J.; Meyers, A. I. *J. Org. Chem.* **1993**, *58*, 3568.

(8) The Advantage Series 2050 manual chemistry synthesizer performs five reactions at five different temperatures simultaneously. The working volume is 5−80 mL, and the reactors may be vacuum purged with inert gas. Reagents are added manually through a top port with a septum cap. Available from Argonaut Technologies; see www.argotech.com.

Published on Web 05/15/2003

10.1021/op034033l CCC: $25.00

Scheme 1. **Synthesis of Oxazolidinone 2**

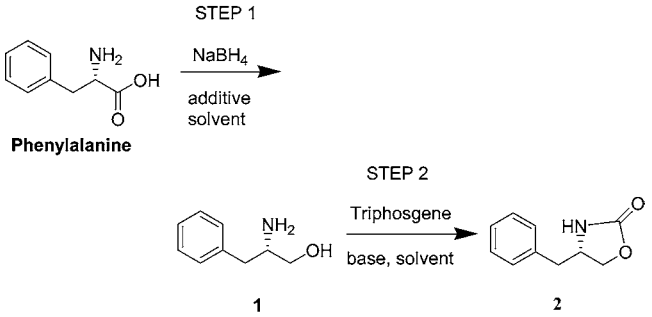


Table 1. **Initial Additive Screen for Step 1**

entry	synthetic notes	% yield[d]	color
1	H_2SO_4 procedure[a]	95	white wax
2	H_2SO_4 procedure	91	white wax
3	H_2SO_4 procedure	91	white wax
4	H_2SO_4 procedure	92	white wax
5	TMS−Cl procedure[b]	0	
6	TMS−Cl procedure	0	
7	TMS−Cl procedure	0	
8	I_2 procedure[c]	94	white solid
9	I_2 procedure	93	white solid

[a] $NaBH_4$ (2.5 equiv), sulfuric acid (1.25 equiv), THF, <20 °C, 16 h. [b] $NaBH_4$ (2.0 equiv), chlorotrimethylsilane (4.0 equiv), THF, 50 °C, 16 h. [c] $NaBH_4$ (2.0 equiv), iodine (1.0 equiv), THF, 20 °C, 16 h. [d] Purity was > 90%, as determined by ^{1}H NMR.

the I_2 reaction were isolated as a free-flowing crystalline solids rather than waxy solids obtained from the H_2SO_4 procedure. Otherwise, the H_2SO_4 and the I_2 procedures were comparable from both a processing and yield perspective.

With these results in hand, we proceeded to test the two superior additives in a one-pot procedure leading to the desired oxazolidinone **2**. The H_2SO_4 and the I_2 procedures detailed previously were followed, and the reactions were quenched with MeOH, to destroy the excess borane, and hydrolyzed with aqueous sodium hydroxide to destroy any borane−amine adducts or borate esters.[9] The reactions were then treated directly with triphosgene[10] (0.35 equiv) for 2 h (step 2), and the product was isolated by extractive aqueous workup with DCM followed by crystallization from EtOAc−hexanes.[11] Two reactions for each additive were conducted with one being worked up at the intermediate alcohol stage, so that the yield for the second step could be estimated. Results are presented in Table 2.

For the sulfuric acid reaction, intermediate **1** was isolated in 90% yield (entry 1), while the oxazolidinone **2** was isolated in 81% yield (entry 2). Therefore, the yield of step 2 was estimated to be 90%. For the iodine reaction, intermediate **1** was isolated in quantitative yield, while the oxazolidinone **2** was isolated in 92% yield. Therefore, the yield of step 2 was again estimated to be 90%. The purity of **2** ranged from 92 to 95%, as determined by ^{1}H NMR spectroscopy. Although not identified, the impurity displayed ^{1}H NMR patterns similar to those of **2** and was quantitated by comparison of the integrals of corresponding peaks. The purity of the **2** from the I_2 reaction was slightly higher, and the material was more crystalline and displayed better filtration rates and bulk handling properties.

Optimization. Since two of the additives gave the desired product in excellent yields, under essentially identical conditions, we considered other factors to make a selection. Balanced equations were constructed to examine raw materials and waste products in more detail (Scheme 2).[12] The reactions are remarkably atom economic with all C-, N-, and O-containing raw materials ending up in the product. The only byproducts are inorganic salts and hydrogen gas. In the H_2SO_4 process, byproducts include 0.5 mol of sodium sulfate and 3 mol of hydrogen for every mole of **2** produced. In the I_2 process, 0.5 mol of sodium iodide and 2 mol of hydrogen are produced. There is less hydrogen gas produced in the I_2 process; however, this advantage is offset by an increased cost of waste disposal (sodium iodide vs sodium sulfate). The cost of sulfuric acid is considerably less than that of iodine; however, the contribution of either additive to overall cost is minimal at relatively low production volumes. The yield, purity, and handling properties were better for the I_2 additive. In light of this analysis, we elected to proceed with the I_2 process for further development.

Up to this point, we had followed the literature precedent for step 1 in choosing a reaction time of 16 h and an amount of $NaBH_4$ at 2.0 or 2.5 equiv. To make the process more efficient, we chose to optimize these parameters utilizing statistical design of experiments (DoE).[13] Step 2 was deemed not to require optimization at this stage because it employed stoichiometric triphosgene and a relatively short reaction time of 2 h. A simple model-robust process-screening design[14] was assembled for step 1, as shown in Table 3.[15] Experiments were run utilizing the AS 2050 manual synthesizer with run details and results shown in Table 4.

Using the % yield data, a response surface model that fit all the data was developed through statistical analysis. Within the variable range studied, time had no effect and the only significant variable was the amount of $NaBH_4$. A response surface plot is shown in Figure 1.

A plateau in the response surface model was observed between 1.6 and 2.0 equiv of $NaBH_4$. This is greater than the theoretical requirement based on the balanced equation shown in Scheme 2. The borane reduction of Phe requires 3 equiv of hydride. The requirement for excess may result from transfer of less than the theoretical 3 hydrides per borane molecule, loss of borane to the headspace, or reaction with adventitious moisture. Going into the validation stage, we elected to use 1.8 equiv of $NaBH_4$ to ensure complete reduction and a reaction time of the minimum 1 h.

(9) This practice is common to all procedures examined to date.
(10) Eckert, H.; Forster, B. *Angew. Chem., Int. Ed. Eng.* **1987**, *26* (9), 894−895.
(11) The cyclization/workup procedure was adapted from one described in ref 3 where diphosgene was employed to cyclize the amino alcohol obtained by borane−DMS/BF_3 reduction.
(12) These equations are of course ideal and assume transfer of three hydrides from each borane molecule.
(13) (a) Box, G. E. P.; Hunter, W. G.; Hunter, J. S. *Statistics for Experimenters*; Wiley: New York, 1978. (b) Carlson, R. *Design and Optimization in Organic Synthesis*; Elsevier: Amsterdam, 1992.
(14) For a discussion of this type of "optimality" experimental design, see: Myers, R. H.; Montgomery, D. C. *Response Surface Methodology*; John Wiley and Sons: New York, 1995; p 458.
(15) The FusionPro software package available from S-Matrix Corporation was utilized for the experimental design and analysis.

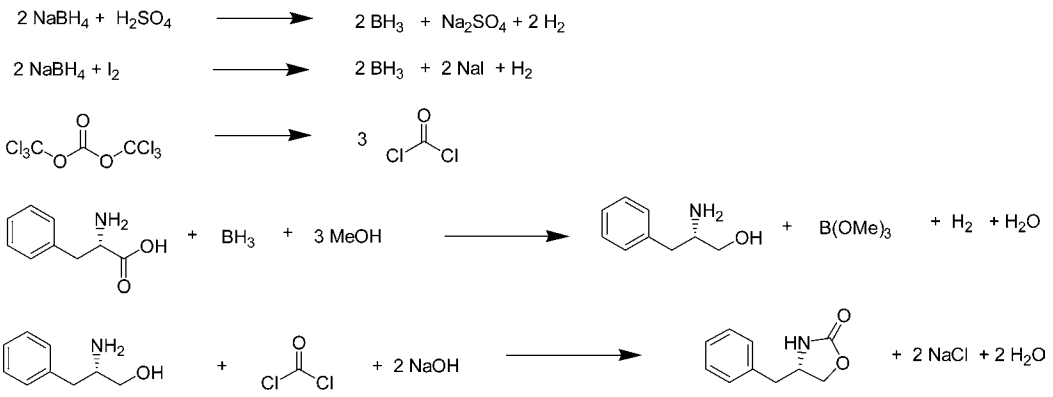
Table 2. **Additive Comparison in the One-Pot Oxazolidinone Synthesis**

entry	additive	triphosgene	% yield step 1	% yield step 2	% yield combined	% impurity[a] ^{1}H NMR	color
1	H_2SO_4	no	90			1.38	white solid
2	H_2SO_4	yes		90[b]	81	7.81	white wax
3	I_2	no	100			1.77	white solid
4	I_2	yes		92[b]	92	4.98	white solid

[a] Determined from the ^{1}H NMR spectrum by integration of an impurity signal at 2.5−2.8 ppm for alcohol or 3.4−3.7 for oxazolidinone. [b] Calculated using the yield for step 1 determined in entries 1 or 3.

Scheme 2. **Relevant Equations for the One-Pot Synthesis of Oxazolidinone 2**

Discrete Reactions:



Balanced Equations:

1 Phe + 1 $NaBH_4$ + 1/2 H_2SO_4 + 1/3 Triphosgene + 3 MeOH + 2 NaOH → 1 oxazolidinone + 1/2 Na_2SO_4 + 1 $B(OMe)_3$ + 3 H_2 + 3 H_2O + 2 NaCl

1 Phe + 1 $NaBH_4$ + 1/2 I_2 + 1/3 Triphosgene + 3 MeOH + 2 NaOH → 1 oxazolidinone + 1/2 NaI + 1 $B(OMe)_3$ + 2 H_2 + 3 H_2O + 2 NaCl

Table 3. **Variables for the Model-Robust Process-Screening Design**

variable name	variable units	range
time	hours	1 < time < 8
amount of $NaBH_4$	equivalents	1.1 < amount of $NaBH_4$ < 2

Table 4. **Run Details and Results of the Model-Robust Process-Screening Design**

run	time	additive (equiv)	$NaBH_4$ (equiv)	% yield	% impurity[a]
1	1	1	2	95	1.81
2	4	0.55	1.1	7	1.74
3	1.8	0.665	1.33	59	6.78
4	1.8	0.89	1.78	99	2.09
5	4	1	2	99	1.57
6	4	0.55	1.1	10	1.14
7	2.5	0.775	1.55	95	5.51
8	4	1	2	96	2.69
9	3.3	0.89	1.78	97	3.29
10	1	0.55	1.1	9	1.91

[a] Determined from the ^{1}H NMR spectrum by integration of the impurity signal at 2.5−2.8 ppm.

Crystallization Study. The usual solvent system reported in the literature for crystallization of the oxazolidinone **2** is ethyl acetate−hexanes and typically results in the recovery of 70% in the first crop. Prior to validation of our process, we conducted a brief crystallization study to determine if improvements could be realized. A series of solvent compositions was initially screened at a small scale (0.25 g in 3 mL vials). Solvents included ethyl acetate, isopropyl acetate, dichloromethane, toluene, and tetrahydrofuran with antisolvents being either hexane or heptane. Of these, isopropyl acetate−heptane and toluene−heptane appeared most promising. These solvents were further screened at the 1.7 g scale utilizing the AS 2050, and results are reported in Table 5.

Experiments were conducted using crude product obtained from the iodine procedure by first dissolving it in DCM to mimic the composition of the crude extract obtained upon workup. The DCM was removed by distillation, and the first solvent was added, so that the final composition would be 3:2 solvent to antisolvent with a total volume of 5 mL per g of product. The original ethyl acetate−hexane conditions were included as a reference standard. In most cases, the product separated out as an oil prior to a rapid crystallization event. All new conditions represented improvement over the original procedure. Both isopropyl acetate−heptane and toluene−heptane gave recoveries approaching 80%. We elected to follow the isopropyl acetate−heptane procedure because the crystals tended not to stick to the vessel walls, thus facilitating isolation.

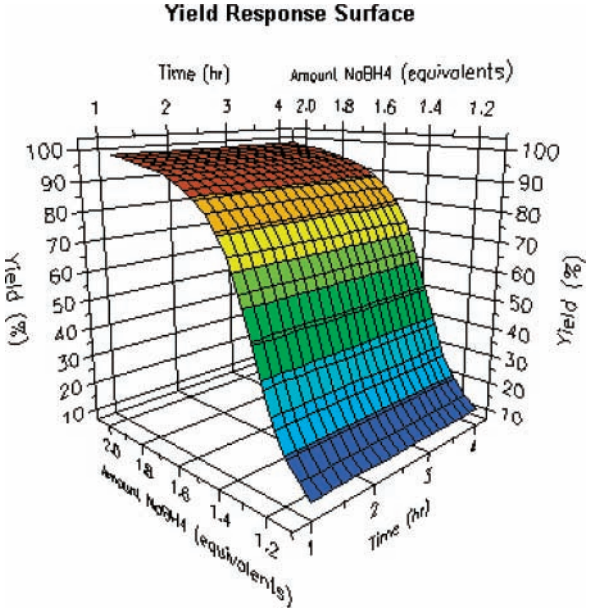


Figure 1. **Response surface diagram from the model-robust process-screening design.**

Table 5. **Recrystallization of Oxazolidinone 2**

first solvent	second solvent	observation	% recovery
EtOAc	hexane	phase separated at ~35 °C; crashed out at ~30 °C	66
^{i}PrOAc	heptane	phase separated at ~35 °C; crashed out at ~30 °C	69
heptane	^{i}PrOAc	cloudy then clear, add 0.1 mL of heptane; fine ppt ~35 °C	79
toluene	heptane	cloudy then phase separated, add 0.2 mL of toluene; crashed out at ~29 °C	77
heptane	toluene	turned clear, add 0.1 mL of heptane; phase separated and crashed out at ~29 °C	78

Validation. With the screening, optimization, and crystallization studies completed, the next step was process characterization and validation. Based on the previously mentioned studies, a recipe was assembled and executed on the fully automatic Advantage Series 3400 Process Chemistry Workstation[16] (AS 3400). The recipe is reproduced in Table 6.

The recipe steps 1−16 were executed, and a process data graph was generated automatically from the run data log (Chart 1). The chart shows the two feeds, the internal reaction temperature, and the calculated heat of reaction[17] plotted versus time for the two feeds and the manually added quench solutions. The feed of the iodine solution was accompanied by a temperature rise due to the exothermic formation of diborane and the subsequent reduction of the carboxylic acid. The total heat of reaction for the reduction step was calculated to be 23 kJ per 8.3 g of Phe or ~450 kJ mol^{-1}. While this is a highly exothermic process, the reaction is rapid with ~70% of the total heat generation occurring during the 20 min feed period. The entire exothermic event was complete within 50 min. This indicates that the reaction is well controlled by adjusting the feed rate and may be scaled-up with relative safety. There is no induction period or apparent accumulation of starting materials or intermediates.[18]

The manual addition of the MeOH quench occurred at about 110 min with a significant release of energy (~160 kJ mol^{-1}). The exotherm was again rapid, indicating that it too could be well controlled by adjusting the feed rate. The subsequent manual addition of the NaOH solution was accompanied by a smaller release of ~50 kJ mol^{-1}.

The subsequent distillation is evident with a visible dip in the reaction temperature curve due to the removal of THF. Following the cooldown to ~5 °C, the spike observed in the temperature curve corresponds to the manual addition of DCM. Following this, the triphosgene solution feed caused a significant heat release of ~420 kJ mol^{-1} due to the nucleophilic addition to triphosgene during the cyclization reaction (double acylation). While this is also a highly exothermic process, the reaction is rapid with ~60% of the total heat generation occurring during the 10 min feed period. The entire exothermic event was complete within 30 min. This indicates that the reaction is well controlled by adjusting the feed rate and may be scaled-up with relative safety. There is no induction period or apparent accumulation of starting materials or intermediates.

Table 6. **Recipe for the One-Pot Synthesis of Oxazolidinone 2**

step	operation	material	settings
1	manual charge	phenylalanine	8.3 g, 1.0 equiv
2	manual charge	THF	50 mL, 6 mL/g of Phe
3	start agitation		800 rpm
4	set temperature		25 °C
5	manual charge	$NaBH_4$	3.4 g, 1.8 equiv
6	temp based feed	I_2 solution	20 mL, 1 mL/min, temp ± 5 °C, 0.9 equiv
7	wait		1 h
8	manual charge	MeOH	10 mL, 5.0 equiv
9	manual charge	20% NaOH	50 mL, 5.0 equiv
10	set temperature	distill organics	to 80 °C
11	set temperature		0 ± 5 °C
12	manual charge	DCM	50 mL, 6 mL/g Phe
13	temp based feed	triphosgene solution	20 mL, 2 mL/min, temp < 30 °C
14	set temperature		25 °C
15	wait		1.5 h
16	stop agitation		0 rpm
17	manual separation	remove aqueous	dry (Na_2SO_4), return to reactor
18	start agitation		150 rpm
19	manual charge	isopropyl acetate	25 mL, 3 mL/g of Phe
20	manual charge	heptane	17 mL, 2 mL/g of Phe
21	set temperature	distill DCM	to 85 °C
22	set temperature		to 0 °C, linear ramp over 2 h
23	stop agitation		0 rpm
24	manual filter	remove product	end

(16) The Advantage Series 3400 Process Chemistry Workstation performs four computer-controlled reactions simultaneously. Each reactor module houses a glass reactor, 130 or 250 mL, and two feed pumps with reservoirs. The reactions may be run according to prewritten recipes or controlled by immediate command of the scientist. All process data (time, temperature, pressure, pH, heat flow, etc.) are logged to a protected run file. Available from Argonaut Technologies; see www.argotech.com.

(17) The AS 3400 calculates the heat of reaction by integration of the area under the heat flow curve with time.

(18) While the absence of observed induction periods or reagent accumulation suggests that the process is suitable for scale-up, it is not definitive proof of its safety. Further hazard analysis testing, such as DSC and ARC, may be required to completely assess the risks prior to plant-scale operations.

Chart 1. **Process Data Graph from the AS 3400**

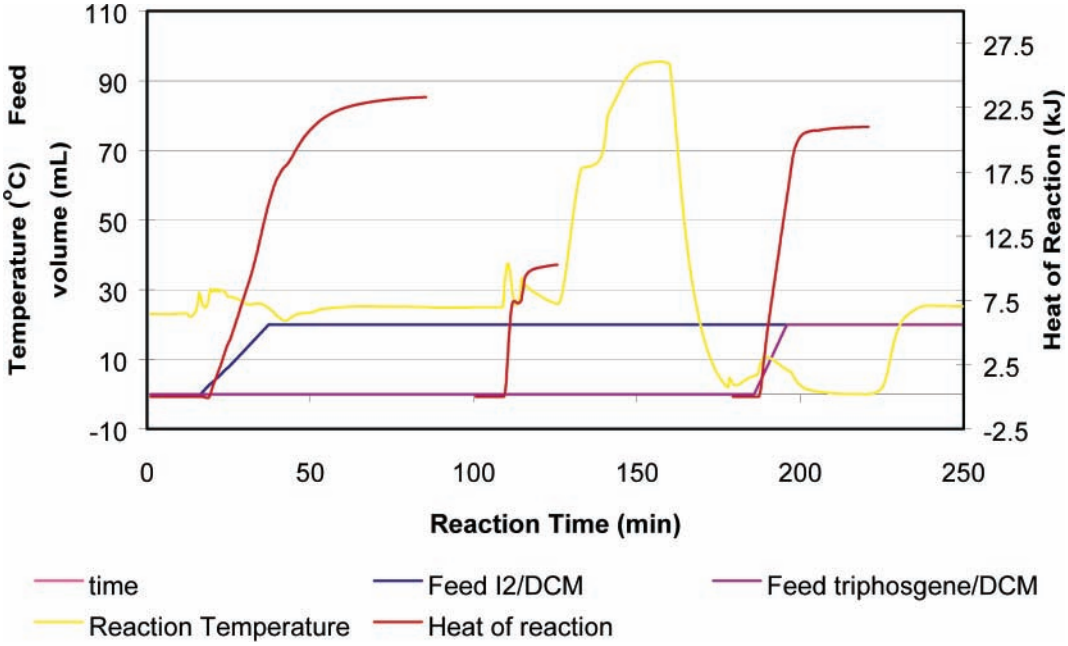
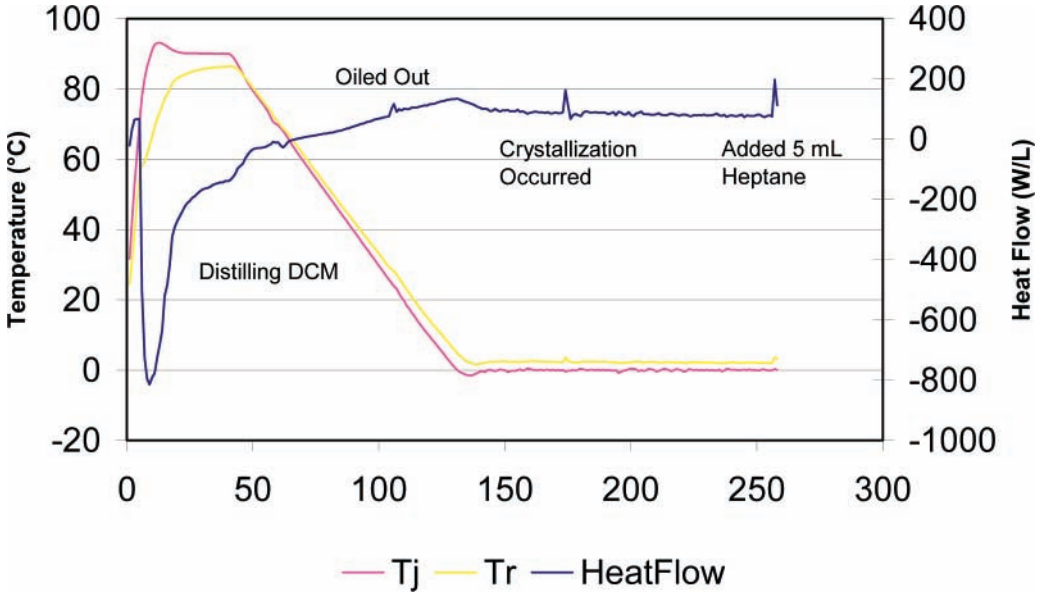


Chart 2. **Crystallization Temperature Profile**



After a 90 min aging period, the crude reaction mixture was removed to extract the product with DCM. The DCM solution was then replaced in the reactor, and steps 19−24 were executed. The reactor and jacket temperature and the heat flow profiles of the crystallization are presented in Chart 2. Starting at ambient temperature, the AS 3400 instrument added isopropyl acetate and heptane, and the solution was heated. Significant heat flow from the jacket to the reactor is noted due to distillation of DCM. Subsequent cooling followed a linear ramp to 0 °C where a small temperature increase was noted upon crystallization. The heat flow curve is more informative showing heat release at ∼30 °C where the product "oiled-out" of solution and a larger heat release where crystallization occurred after the reactor reached 0 °C. After aging 2 h, the solid product was collected by filtration and dried to afford 6.5 g, 74% as a white crystalline solid. The chemical purity was judged to be 97%, as determined by HPLC.

Process Transfer. The transfer of chemical procedures and processes between different site locations is a routine activity within large organizations. This is typically accomplished through lengthy technology transfer documents and/or site visits. Moreover, technology transfer can be a lengthy and time-consuming process that can result in project delays. Therefore, techniques that can facilitate this process are of great interest.

The process recipe shown in Table 6 is a self-contained description of the entire process that was developed herein. The process recipe is an electronic file that is stored along with the measured process data at the conclusion of each AS 3400 run. To show process transferability, this file was sent via email from our Foster City, California facility to

Table 7. **Original Preparation vs Subsequent One-Pot Syntheses of Oxazolidinone 2**

reference	reducing agent (equiv)	yield	cyclization agent	yield	comments	waste generated
Evans, 1989, ref 2	BH_3−DMS (1.15), BF_3−OEt_2 (1.0), reflux 6 h	74% in two crops	diethyl carbonate (20), K_2CO_3 (0.1), 135 °C, 2.5 h, distill EtOH	79% crystallization (58% overall)	induction period, violent exotherm, two isolations, high temp distillation, DMS stench	H_2, DMS, borates, EtOH, diethyl carbonate
Pridgen, 1989, ref 3	BH_3−DMS(1.6) BF3−OEt_2 (1.23), reflux 3 h	one pot	diphosgene (0.6), −20−20 °C, 2 h	78% crystallization	induction period, violent exotherm, DMS stench	H_2, DMS, borates, NaCl
Greene, 1991, ref 4a	lithium aluminum hydride (2.0), reflux 6 h	one pot	triphosgene (0.47), −5−20 °C, 3 h	80% chromatography	LAH hazards, difficult isolation, Al salt waste	H_2, aluminum salts, NaCl, chrom. solvents
Gooding, 2003	$NaBH_4$ (1.8), I_2 (0.9), 25 °C, 1 h	one pot	triphosgene (0.34), 0−20 °C	74% crystallization	use of I_2, exotherms well controlled by feed rates	H_2, borates, NaI, NaCl

our Indianapolis, Indiana facility where it was executed by a different scientist on a different AS 3400 system. This experiment went smoothly with minimal verbal interaction between the two locations. The desired product was isolated in 72% yield, and the process data from each of the two runs were in good agreement.

Comparative Analysis. The original Evans procedure employed the borane−DMS complex in the presence of BF_3 etherate in the reduction step. Although efficient, this complex liberates malodorous and volatile dimethyl sulfide upon reaction that must be scrubbed when working at a large scale. The BF_3 etherate additive is expensive and moisture sensitive. This reduction was also found to exhibit induction periods and potentially violent exotherms, making the prospect for scale-up quite ominous. Following isolation of the intermediate amino alcohol, the cyclization step employed diethyl carbonate as reagent and solvent. The reaction was driven to completion by distillation of the byproduct ethanol. This process was energy intensive requiring a 6 h reflux for the reduction followed by a 135 °C distillation for the cyclization. Product was isolated in 58% yield (Table 7).

The Pridgen procedure made several improvements over the original Evans method. Although the same reagents were employed for the reduction, the problems of induction periods and exotherms were addressed prior to scale-up. The solvent system was changed from THF to ethylene glycol dimethyl ether, so that the reducing agent could be added at a higher temperature to prevent build up of high energy intermediates. This procedure employed diphosgene in place of excess diethyl carbonate in the cyclization step and was conducted without isolation of the intermediate amino alcohol. Although greatly improved, the process still had the same drawbacks associated with the use of the borane−DMS complex in the presence of BF_3 etherate in the reduction step. The yield was improved to 78% (Table 7).

The Greene procedure was operationally similar to the Pridgen procedure with the following exceptions: (1) borane−DMS/BF_3 etherate was replaced with lithium aluminum hydride (LAH); (2) diphosgene was replaced with triphosgene. Although LAH offers some advantages over borane−DMS/BF_3 etherate, it presents other issues associated with its safe handling and use. It is extremely moisture sensitive and is well-known to present workup and waste disposal challenges related to the formation of aluminum salt byproducts. Its use at a large scale is generally avoided where possible. Isolation in 80% yield required chromatography.

The current procedure makes use of inexpensive $NaBH_4$ as a hydride source and replaced the malodorous borane−DMS/BF_3 etherate additives with I_2. This additive cleanly generated diborane that rapidly completed the reduction of Phe at ambient temperature. There were no dangerous induction periods observed, and the reduction was complete in 1 h. Upon quenching the reaction with methanol and treatment with aqueous NaOH, the cyclization was effected using stoichiometric (0.34 equiv) triphosgene. The product was then isolated in 74% yield by crystallization from isopropyl acetate−heptane. The entire process was conducted in a single reactor, and the byproducts consisted of only inorganic salts and hydrogen gas.

Conclusions

A new and efficient "one-pot" process for the synthesis of (*S*)-4-(phenylmethyl)-2-oxazolidinone has been developed. The first step in the process employed a sodium borohydride reduction of phenylalanine mediated by iodine. The second step utilized triphosgene as a phosgene source to effect cyclization of the intermediate amino alcohol. Both chemical steps and workup procedures were rapidly screened and optimized utilizing statistical design of experiments (DoE) and parallel synthesis. The procedure was further characterized in an automated reactor system that provided heat flow measurements and heat of reaction calculations. Simple examination of the data charts revealed significant information about the process. Three of the process steps were highly exothermic; however, there were no apparent induction periods or accumulation. Both reactions were demonstrated to be feed-controlled. The efficiency of this process compares favorably to those of others previously reported on the basis

of raw material cost, time requirements, reaction hazards, and waste generation.

Experimental Section

The starting materials were purchased from commercial sources and used without further purification. ^{1}H NMR spectra were recorded on a Varian 300 MHz system. The chemical shifts are reported in ppm relative to the solvent residue proton signal ($CDCl_3$ $\delta = 7.28$ ppm). Chemical purity was determined by HPLC (column, Alltech 53 × 7 mm^2 Rocket with Platinum EPS 100A C18; eluent, gradient of acetonitrile/water (10% to 100% over 4 min); flow rate, 3 mL/min; detection at 254 nm). Enantiometric purity was determined by HPLC (column, 250 × 4.6 mm^2 Chiralpak AD; eluent, methanol/hexanes 6:4; flow rate, 1 mL/min; detection at 254 nm).

Reactions on Advantage Series 2050. A. (*S*)-(+)-2-Amino-3-phenyl-1-propanol (1). A typical procedure is described for the optimization reactions described in Table 4. Five dry reactors equipped with septum caps were set up on the AS 2050. Each reactor was charged with L-phenylalanine (1.66 g, 10 mmol) followed by 8.0 mL of THF. The agitation was set to 1000 rpm, the temperature was set to 25 °C, and the mixture was stirred until the temperature equilibrated. Each reactor was then charged with the appropriate amount of $NaBH_4$ (0.42 g, 11 mmol to 0.76 g, 20 mmol) as described in Table 4. **Caution: hydrogen gas evolution!** Five solutions of I_2 (5.5 mmol to 10 mmol) each in 4 mL of THF were prepared in 5 mL polyethylene syringes equipped with a stopcock and needle. The I_2 solutions were added dropwise to the L-Phe mixture through the septum over 30 min. **Caution: formation of borane!** After the addition, the reaction mixture was stirred at 25 °C for 1−4 h as required. After the reaction time, 2 mL of methanol was slowly added, followed by 10 mL of 20% aqueous NaOH solution. The reactor tops were removed, and the mixture was heated by adjusting the setpoint to 110 °C while allowing the solvent (THF) to distill (evaporate). The setpoint was changed to 20 °C, and to the cooled reaction vessel was added 15 mL of water. The mixture was extracted with 4 × 4 mL of DCM, and the combined extract was passed through a 1 g basic alumina column (Argonaut, PN 715-0100-C) attached to an Na_2SO_4 drying plug (Argonaut PN, 802-0250-M). The solvent was then removed in vacuo to obtain the product as a white solid. ^{1}H NMR ($CDCl_3$) δ 2.35 (dd, 1H), 2.65 (dd, 1H), 2.90−3.00 (m, 1H), 3.15 (dd, 1H), 3.48 (dd, 1H), 7.0−7.2 (m, 5H).

B. (*S*)-(−)-4-Benzyl-2-oxazolidinone (2). A typical procedure is described for Table 2, entry 4. The reduction of Phe was conducted as described previously through the addition of NaOH solution. The setpoint was adjusted to 85 °C with the vessel's cap open to distill out the organic solvent. The reactor was then cooled by changing the setpoint to 0 °C. The mixture was diluted with 10 mL of DCM and equilibrated at 0 °C. A solution of triphosgene (1.0 g, 3.4 mmol) in 5 mL of DCM was added dropwise through the septum cap over 30 min. After the addition, the reaction was stirred at 25 °C for 2 h. Water was added (15 mL), and the mixture was extracted with 4 × 4 mL of DCM. The combined extract was passed through an Na_2SO_4 drying plug, and the solvent was then removed in vacuo to obtain the product as a white solid or colorless wax, depending on the additive. The crude product was recrystallized from ethyl acetate/hexanes (1:2). ^{1}H NMR ($CDCl_3$) δ 2.71 (d, 2H), 3.90−4.10 (m, 2H), 4.31 (t, 1H), 5.10−5.28 (m, 1H), 7.1 (d, 2H), 7.1−7.21 (m, 3H). 100% S-enantiomer, as determined by chiral HPLC.

Reactions on Advantage Series 3400. Procedure for One-Pot Synthesis of 2. A 125 mL reactor was installed on an AS 3400 module. The pumps were primed with the appropriate solution: iodine (12.7 g, 50 mmol) in 20 mL of THF was loaded onto the Feed A position, and triphosgene (5.0 g, 17 mmol) in 20 mL of DCM was loaded onto the Feed B position. The recipe for the synthesis, as shown in Table 6, was activated with a 15 s data logging interval. The recipe executed automatically, and the instrument cued the operator on all of the steps requiring manual intervention. Following step 16, the reaction mixture was transferred to a separatory funnel and the aqueous layer was discarded. The organic layer was dried (Na_2SO_4) and replaced in the reactor. The recipe was resumed for the crystallization process. After step 24, the reactor was opened and the product was collected by filtration and dried to constant weight in a vacuum oven affording 6.5 g as a white crystalline solid. The product had physical properties identical to authentic samples obtained from commercial sources. The chemical purity was >97%, and the enantiopurity, >99%, as determined by HPLC, as described previously. The graphs shown in Charts 1 and 2 were obtained from the run report generated automatically at the conclusion of the experiment.

Received for review February 25, 2003.

OP034033L