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One-Pot Process for the Preparation of a β-Alkynyl β-Amino Acid Ester

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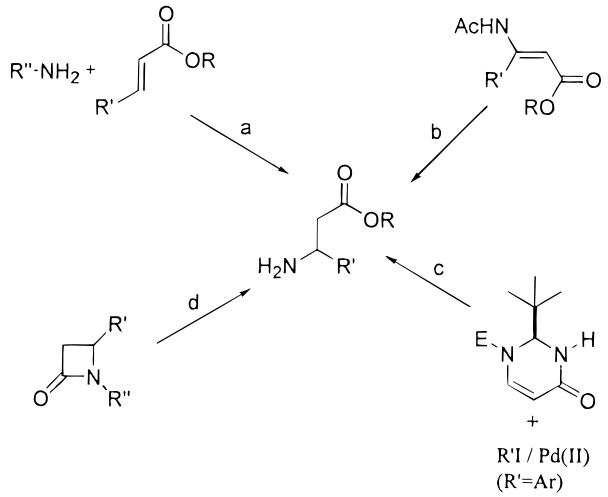
Abstract:

The large-scale preparation of the β-alkynyl β-amino acid ester (±)-1,1-dimethylethyl 3-amino-5-(trimethylsilyl)-4-pentynoate (A) is discussed. It was discovered that addition of a catalytic amount of lithium bis(trimethylsilyl)amide (LHMDS) to a mixture of *tert*-butyl acetate and *N*,3-bis(trimethylsilyl)-2-propyn-1-imine (B) initiated a self-perpetuating reaction and gave high yields of the β-amino ester A upon quench. This one-pot procedure eliminated the need to prepare the unstable lithium *tert*-butyl acetate in a separate reactor and enabled the reaction to be scaled up and run at a more acceptable process temperature (−20 °C) compared to the analogous two-pot reaction (−45 °C). Addition of 3-(trimethylsilyl)-2-propynal to LHMDS in THF at −20 °C followed by chlorotrimethylsilane formed the imine B *in situ*. *tert*-Butyl acetate (6 equiv) was added followed by a substoichiometric quantity (0.15−0.20 equiv) of LHMDS. After quenching with aqueous ammonium chloride the product A was obtained in a yield averaging 70%.

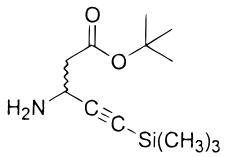
Background

The use of β-amino acids has become an important tool in the development of peptidomimetics,[2] functionalized β-lactams,[3] and some naturally occurring alkaloids and antibiotics.[4] Consequently, considerable effort has been spent in developing synthetic methods for the preparation of β-amino acids.[5] Scheme 1 illustrates four common approaches toward the preparation of this important class of compounds. A large part of the published work has focused on the preparation of α,β-disubstituted β-amino acids. Most recently, much effort has been directed toward the synthesis of the paclitaxel side chain, (2*R*,3*S*)-β-amino-α-hydroxyhydrocinnamic acid, which has been shown to be a necessary feature for biological activity.[6] Thus far, however, there have been relatively few reports on the production of β-amino acids in multikilogram quantities.[7]

Scheme 1



Our interest in this class of compounds stemmed from the need for us to produce the β-alkynyl β-amino acid ester **1** in 100 kg quantities. We quickly ruled out the four generic



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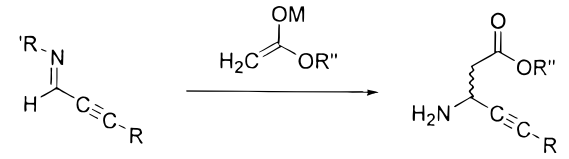
approaches depicted in Scheme 1 because of (i) a lack of selectivity between the catalytic reduction of alkynes and the hydrogenolysis of benzyl moieties (route a),[8] (ii) a lack of selectivity between reducing alkynes and enamines (route b),[9] (iii) a lack of precedent for substituting an alkyne for an aryl iodide (route c),[10] and (iv) the difficulty in preparing 4-alkynyl-substituted 2-azetidinones (route d).[11] The condensation reaction between ester enolates and imines to form β-amino acids and their derivatives had considerable precedent.[11,12] Consequently we decided to investigate the general reaction sequence depicted in Scheme 2, the addition of an ester metal enolate to an aldimine.

The Original Process

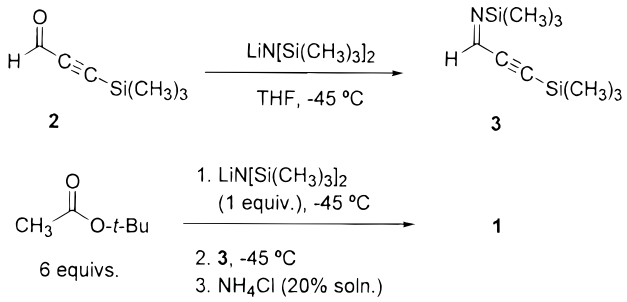
The methodology used to prepare **1** initially consisted of a two-pot reaction sequence as shown in Scheme 3. The

(1) Current address: Ligand Pharmaceuticals, San Diego, CA.
(2) Juan, X.; Soleilhac, J. M.; Schmidt, C.; Peyroux, J.; Roques, B. P.; Fournié-Zaluski, M. C. *J. Med. Chem.* **1989**, *32*, 1497.
(3) Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G.; Bouffard, F. A. *J. Am. Chem. Soc.* **1980**, *102*, 6161.
(4) *Chemistry and Biochemistry of the Amino Acids*; Barrett, G. C.; Ed.; Chapman and Hall: New York, 1985.
(5) (a) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517. (b) Juarista, E.; Quintana, D.; Escalante, J. *Aldrichimica Acta* **1994**, *27*, 3.
(6) For examples, see: (a) Gennari, C.; Vulpetti, A.; Donghi, M.; Mongelli, N.; Vanotti, E. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1723. (b) Hattori, K.; Miyata, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 1151. (c) Hattori, K.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 2785. (d) Jefford, C. W.; Wang, J. B.; Lu, Z. *Tetrahedron Lett.* **1993**, *34*, 7557. (e) Georg, G. I.; Cheruvallath, Z. S.; Harriman, G. C. B.; Hepperle, M.; Park, H. *Biorg. Med. Chem. Lett.* **1993**, *3*, 2467. (f) Nicolau, K. C.; Dai, W. M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15. (g) Rey, A. W.; Droghini, R.; Douglas, J. L.; Vemishetti, P.; Boettger, S. D.; Saibaba, R.; Dillon, J. L. *Can. J. Chem.* **1994**, *72*, 2131.
(7) A multikilogram synthesis of a precursor to the paclitaxel side chain has been reported; see ref 6g.
(8) (a) d'Angelo, J.; Maddaluno, J. *J. Am. Chem. Soc.* **1986**, *108*, 8112. (b) Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1991**, *2*, 183.
(9) Lubell, W. D.; Kitamura, M.; Noyori, R. *Tetrahedron: Asymmetry* **1991**, *2*, 543.
(10) (a) Chu, K. S.; Konopelski, J. P. *Tetrahedron* **1993**, *49*, 9183. (b) Chu, K. S.; Negrete, G. R.; Konopelski, J. P.; Lakner, F. J.; Woo, N. T.; Olmstead, M. M. *J. Am. Chem. Soc.* **1992**, *114*, 1800.
(11) For examples, see: Hart, D. J.; Ha, D. C. *Chem. Rev.* **1989**, *89*, 1447.
(12) Brown, M. J. *Heterocycles* **1989**, *29*, 2225.

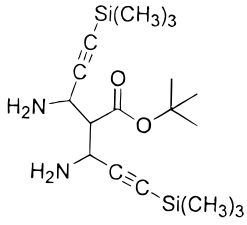
Scheme 2



Scheme 3



known imine **3**[13] was generated in one reaction vessel by treatment of 3-(trimethylsilyl)-2-propynal (**2**)[14] with lithium bis(trimethylsilyl)amide (LHMDS) in THF at −45 °C. In a separate vessel, the lithium enolate of *tert*-butyl acetate (TBA) was generated from an excess of TBA and LHMDS in THF at −45 °C. The imine solution was then added to the enolate solution at −45 °C. The reaction was quenched with aqueous ammonium chloride solution. After workup the solvent was removed by vacuum distillation, and the product was obtained as a dark colored oil (30−35 wt %) in molar yields of 60−70%. The excess of TBA proved to be necessary to achieve good yields, because the bis-addition product **4** became a major side product at low TBA levels. A rationale for this effect of excess TBA will be discussed later (*vide infra*).



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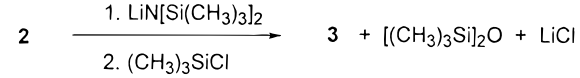
For this process to be successful it was important for the reaction temperature to be maintained at −45 °C or below. All attempts to run the process at higher temperatures gave extremely low yields. In addition it was important that the addition/hold times not exceed 1 h since this also had a detrimental effect on yield.

Due to the limited cooling capability of our larger reactors the two-pot process could not be run on a scale larger than 50 gal. This required us to run multiple small batches (30−50 gal scale) in order to produce >200 kg of **1**. Each batch produced only 8 kg of **1**, requiring 25 batches to be run in order to produce the desired quantity of material. Since it was predicted that 1000 kg quantities would be required in the future (requiring about 125 batches), it was critical that a process be developed to run at higher temperatures in our larger reactors.

Scheme 4



Due to the cooling limitations of our larger equipment, the reaction needed to be run at −20 °C or higher. In addition, the reaction would need to tolerate long addition and hold times. For example, in order to maintain the batch at −20 °C at the 750 gal scale, an addition time of about 2 h would be required (due to the exothermic nature of the reactions). To determine if this was feasible required knowledge of the stabilities of lithium *tert*-butyl acetate (LTBA) and the imine **3** at these reaction temperatures.

Imine Stability

The literature suggested that the imine **3** was thermally stable.[13] If the reaction mixture was quenched with chlorotrimethylsilane (TMSCl), the imine was stabilized and could be isolated in a relatively pure state by vacuum distillation.[13] The imine rapidly decomposed when exposed to air or moisture. However, if stored at temperatures <5 °C under an atmosphere of nitrogen, the imine was a solid and was stable for several days. The enhanced stabilization by TMSCl was postulated to be the result of quenching of the lithium trimethylsilanolate by-product formed during the formation of **3** to give hexamethyldisiloxane (HMDO) and lithium chloride (Scheme 4). The imine **3** along with the HMDO by-product could be observed by GC. The identity of the imine **3** was confirmed by GC/MS, while the HMDO had a retention time matching that of an authentic standard.

Enolate Stability

The stability and structure of lithium ester enolates has been the focus much attention.[15] It was reported that solutions of LTBA in THF generated from TBA and LHMDS at −60 °C decomposed when allowed to warm to 23 °C.[15a] The decomposition product was assigned as the enolate of *tert*-butyl acetoacetate using ^{1}H NMR. In addition, a solution of LTBA in THF generated using lithium *N*-isopropylcyclohexylamide (LICA) was reported to decompose with first-order kinetics at 23 °C.[15a] However, a separate study reported that ester enolates generated in THF using LICA at −78 °C were stable when warmed to ambient temperature.[15b] Some lithium ester enolates have been isolated in the solid state and characterized.[15a,c,f,g] This was accomplished by utilizing a nonpolar solvent such as hexane from which they precipitate.

On the basis of these reports we initially investigated the use of hexane as a solvent or LICA as base to see if either

(13) Colvin, E. W.; McGarry, D.; Nugent, M. J. *Tetrahedron* **1988**, *44*, 4157 and references therein.

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(15) (a) Sullivan, D. F. The Reactions of Ester Enolates. PhD Dissertation, Michigan State University, 1974; *Diss. Abstr. Int., B* **1975**, *36*, 248. (b) Rathke, M. W.; Lindert, A. *J. Am. Chem. Soc.* **1971**, *93*, 2318. (c) Rathke, M. W.; Sullivan, D. F. *J. Am. Chem. Soc.* **1973**, *95*, 3050. (d) Sullivan, D. F.; Woodbury, R. P.; Rathke, M. W. *J. Org. Chem.* **1977**, *42*, 2038. (e) Häner, R.; Laube, T.; Seebach, D. *J. Am. Chem. Soc.* **1985**, *107*, 5396. (f) Seebach, D.; Amstutz, R.; Laube, T.; Schweizer, W. B.; Dunitz, J. D. *J. Am. Chem. Soc.* **1985**, *107*, 5403. (g) Kim, Y. J.; Bernstein, M. P.; Galiano Roth, A. S.; Romesberg, F. E.; Williard, P. G.; Fuller, D. J.; Harrison, A. T.; Collum, D. B. *J. Org. Chem.* **1991**, *56*, 4435.

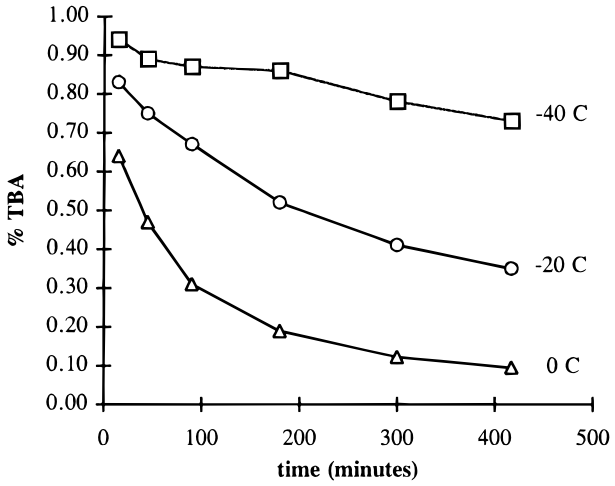


Figure 1. **Decomposition of LTBA in THF. TBA was added to LHMDS at the temperatures shown, and aliquots were withdrawn and quenched at selected time intervals. The recovered TBA was quantitated versus an internal standard.**

would allow the reaction to proceed at higher temperatures. Unfortunately these attempts met with unmitigated failure. We therefore decided to carry out some LTBA stability studies of our own in order to gather more data. A summary of our enolate stability studies is shown in Figure 1. For these studies, TBA was added to the base at the temperature indicated. Aliquots were withdrawn at various time intervals and quenched into saturated aqueous ammonium chloride. The amount of TBA recovered was analyzed by gas chromatography with the aid of an internal standard (decane). Both TBA and decane displayed linear response behavior in the concentration ranges employed. This study assumed that TBA was quantitatively converted to enolate. As the data in Figure 1 shows, the lithium enolate generated using LHMDS in THF is relatively stable below −40 °C, but decomposes with increasing rapidity above this temperature. In all of these runs, the self-condensation product of TBA (*tert*-butyl acetoacetate) was also quantitated and accounted for the majority of the enolate decomposition. The mechanism of this decomposition was not fully understood; however, there have been several mechanisms postulated for the decomposition of ester enolates.[15a] All of the proposed decomposition routes would lead ultimately to *tert*-butyl acetoacetate or its salt.[15a] It was shown that an ester enolate can undergo a unimolecular decomposition to a ketene and an alkoxide; however, it was not proven that LTBA decomposes via this pathway.[15a,d−f] Our results do not display simple kinetics, and so it was possible that more than one mechanism was operating.

Conclusions: Enolate/Imine Stability

It was clear that enolate stability was the limiting factor in developing a process which could be run at a higher temperature (*vide supra*). It was thus apparent that a means of mitigating the enolate instability was essential for success. We deduced that the only means of carrying out this transformation on a larger scale would be a one-pot reaction wherein the enolate was generated *in situ* or through the use of a continuous flow reactor.

Table 1. **Screening experiments for a one-pot reaction**

line no.	addn time to form imine **2** (h)	temp (°C)	TMS-Cl[a]	TBA (equiv)	addn time for condensation (h)	temp (°C)	yield (%)
1	1.5	−15	Y	5	3	−20	36
2	0.1	−15	Y	5	0.25	−20	43
3	1.5	−10	N	6	1.5	−10	34
4	1.5	−10	Y	6	1.5	−10	48

[a] Y, yes; N, no.

Table 2. **Factors and ranges for the 2^{4-1} fractional factorial design**

factor	unit	low setting	high setting
temp (imine formation)	°C	−20	−10
tert-butyl acetate	equiv	4	8
LHMDS (imine formation)	equiv	0.9	1.1
temp (condensation)	°C	−20	−10

Studies on the One-Pot Reaction

Screening experiments were performed, in which an excess of TBA was mixed with the preformed imine **3** followed by addition of 1 equiv of LHMDS. The reaction was quenched with aqueous ammonium chloride as for the two-pot reaction. The results of these initial screening reactions are shown in Table 1. A moderate yield could be obtained at a higher temperature (−10 to −15 °C). It was also observed that longer addition times were tolerated reasonably well (lines 1 and 2) and that addition of TMSCl had a positive effect on the yield (lines 3 and 4).

A detailed study of the reaction, using TMSCl to stabilize the imine **3**[13] and incorporating statistical design of experiments (DOE),[16] was conducted. A 2^{4-1} fractional factorial design,[16] including center points, was initially carried out. The assumption was made at this point that 1 equiv of LHMDS would be required for the condensation reaction, and so this factor was held constant. The factor and range table for this design is shown in Table 2, and the full design table with results is shown in Table 3. Computation of the data generated the effects shown in Table 4. Using a normal probability plot[16] it was judged that the effects *B* (equivalents to TBA), *C* (equivalents of LHMDS), and *A* (temperature during imine formation) were active. With the reduced number of factors the design was collapsed to a 2^3 factorial, which could be presented in a cube format (Figure 2). The region around the rear, upper left corner of the cube showed the greatest promise (53 % yield) and was explored more thoroughly by construction of a central composite design around this point.[17] The TBA and LHMDS levels were varied at a constant temperature of −20 °C. The additional design table with results is shown in Table 5. The three-dimensional plot in Figure 3 depicts the reaction surface. The optimum amount of LHMDS appeared to be around 1.1 equiv, and the yield increased with increasing TBA although

(16) (a) Morgan, E. *Chemometrics: Experimental Design*; John Wiley & Sons: New York, 1995. (b) Box, G. E. P.; Hunter, W. G.; Hunter, J. S. *Statistics for Experimenters: An Introduction to Design, Data Analysis and Model Building*; John Wiley & Sons: New York, 1978.
(17) Box, G. E. P.; Wilson, K. B. *J. R. Stat. Soc. B* **1951**, *13*, 1.

Table 3. **Design table and results for the 2^{4-1} fractional factorial design**

A: temp imine (°C)	*B*: *tert*-butyl acetate (equiv)	*C*: LHMDS imine (equiv)	*D*: temp conden (°C)	yield (%)
−20	4	0.9	−10	24
−10	4	0.9	−20	30
−20	8	0.9	−20	36
−10	8	0.9	−10	29
−20	4	1.1	−20	43
−10	4	1.1	−10	33
−20	8	1.1	−10	53
−10	8	1.1	−20	42
−15	6	1.0	−15	44
−15	6	1.0	−15	43

Table 4. **Calculated effects for the 2^{4-1} fractional factorial design**

term	coeff	sum sqr
A	−5.5	61
B	7.5	113
C	13.0	228
D	−3.0	18
AB	−3.5	25
AC	−5.0	50
AD	−2.0	8

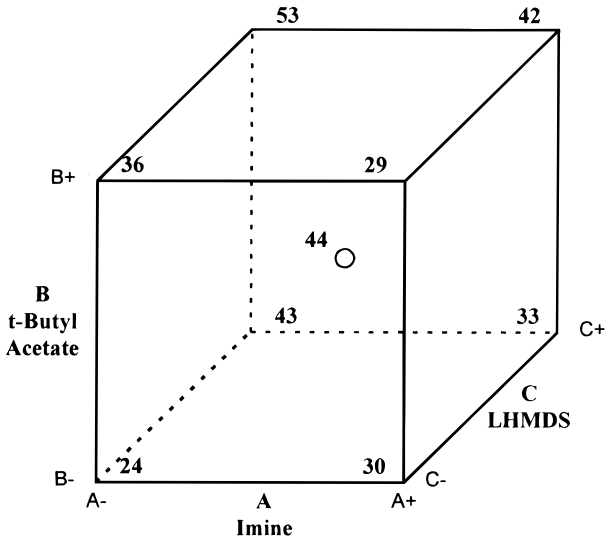


Figure 2. **Cube plot of data from the collapsed 2^3 factorial design.**

the yield improvement diminished around 10−12 equivs.[18] Molar yields of 61−63% were obtained, which approached the molar yields obtained in the plant for the two-pot process (average = 70%).

Calorimetry Study and Mechanistic Interpretation

Prior to piloting these conditions in the plant, a calorimetry study was carried out to determine if any potentially hazardous exotherms would be encountered upon scaleup and to gain kinetic information about the process. The imine formation and TMSCl addition displayed normal dose-controlled characteristics over the addition times employed (about 2 h and 40 min, respectively), with heat output being proportional to the addition rate of the reagents. The heat output from the second LHMDS addition was anomalous, however, and is shown in Figure 4.

A "spike" in the heat output was observed at 0.1−0.2 equiv of LHMDS with little heat evolved before or after that point. This observation allowed us to postulate that the reaction was complete after approximately 0.2 equiv of LHMDS had been added. In order to confirm this hypothesis a reaction was performed with 0.3 equiv of LHMDS (for the condensation) and 12 equiv of TBA. Analysis of the

(18) The aldehyde **2** was obtained as a 50−60% solution in MTBE, and the process was optimized using this crude material.

Table 5. **Results to extend the 2^3 factorial design to a central composite design[a]**

tert-butyl acetate (equiv)	LHMDS (equiv)	yield (%)
6	1.0	41
10	1.0	53
6	1.2	39
10	1.2	44
4	1.1	43
12	1.1	62
8	0.9	36
8	1.3	39
8	1.1	53

[a] Temperature constant at −20 °C.

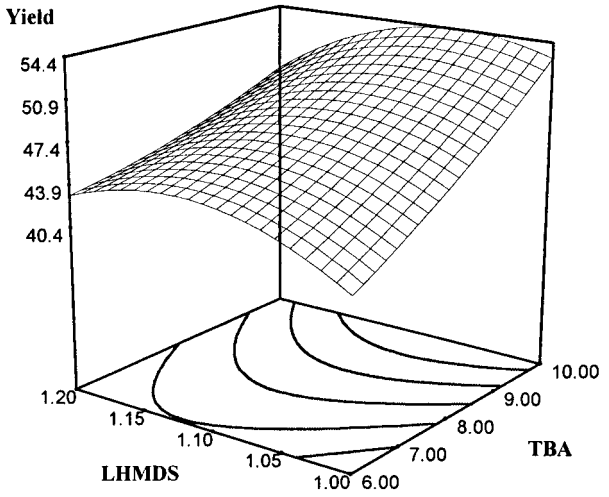


Figure 3. **Three-dimensional plot of the central composite experimental design (contour lines represent approximately 2% unit changes).**

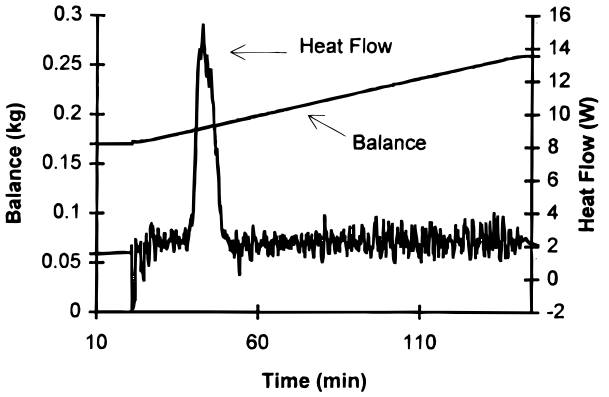
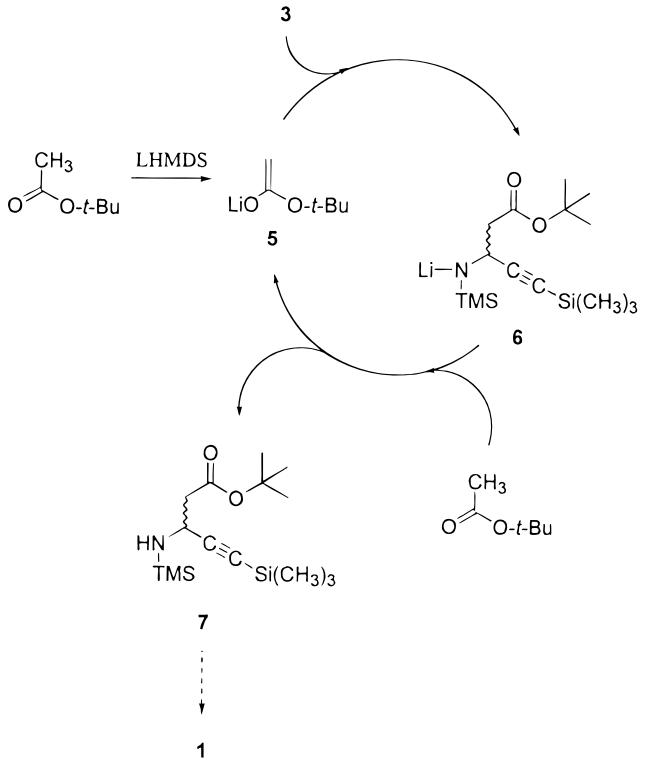


Figure 4. **Heat flow from the addition of LHMDS for the condensation reaction.**

Scheme 5



reaction mixture by GC indicated that the imine **3** was consumed. After quenching of the reaction, a molar yield of 76% was obtained.

A probable mechanism is shown in Scheme 5. LHMDS acted as an initiator for a self-perpetuating reaction. The LTBA **5** was generated, which was trapped by the imine **3** to give the condensation product **6**. Because the basicity of **6** was similar to that of LHMDS, it was able to deprotonate another molecule of TBA to form more **5**, which continued the cycle. The cycle was repeated until all of the imine **3** was consumed. The *N*-TMS intermediate **7** was desilylated upon quench, providing the desired β-amino ester **1**. This scheme accounted for the observation that excess TBA is beneficial to the reaction yield. The TBA acted as a proton source[13] and effectively competed for reaction with *N*-lithio species **6**, which could otherwise undergo an undesirable side reaction leading to the bis-addition product **4** (Scheme 6).[19]

Optimization of the One-Pot Process

To study the variation of TBA and LHMDS (for the condensation) stoichiometries, a replicated 2^2 factorial design with center points was performed (since both reagents were involved in the mechanistic model). An interaction effect between these two factors was observed (Table 6). A three-dimensional contour plot of the data (Figure 5) indicates that the process performs best along a diagonal from low settings of TBA and LHMDS to high settings of TBA and LHMDS. At high TBA and low LHMDS the reaction was not reproducible, and the yield varied between 0% and 69% (Table 6). GC analysis of the reaction mixture prior to quench revealed incomplete consumption of the imine **3**. Thus, at a high level of TBA a higher level of LHMDS was needed to drive the reaction to completion. At low levels of TBA the yield gradually decreased with increasing LHMDS. With the low level of TBA a greater overall throughput was obtained albeit with a slightly lower yield. Accordingly, efforts were focused around the region of 6

(19) The bis-addition product **4** was not observed as an impurity in the optimized one-pot process.

Scheme 6

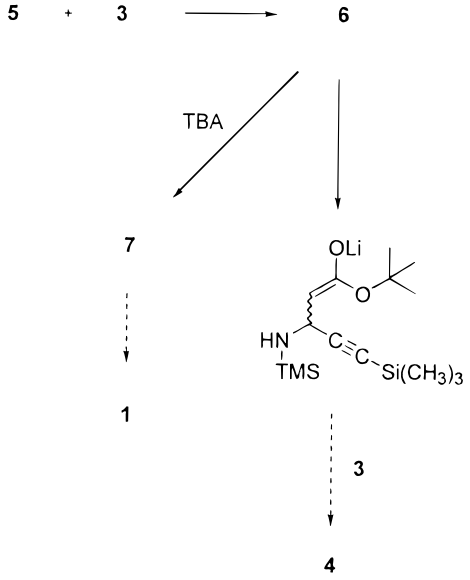


Table 6. **Results for the replicated 2^2 factorial design**

tert-butyl acetate (equiv)	LHMDS (equiv)	yield (%)
6	0.15	71
6	0.15	72
6	0.15	66
12	0.15	69
12	0.15	33
12	0.15	0
6	0.3	61
6	0.3	64
12	0.3	76
12	0.3	72
10	0.23	74
10	0.23	70

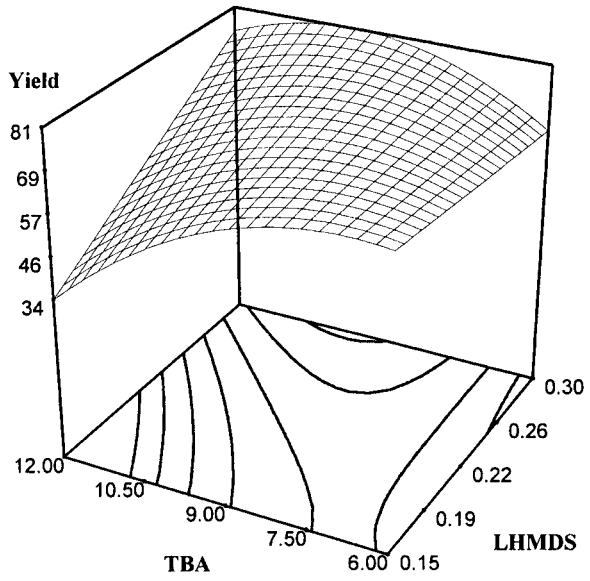


Figure 5. **Three-dimensional plot of the replicated 2^2 factorial design (contours represent 5% unit changes).**

Table 7. **Results for the extended 2^2 factorial design**

TMSCl (equiv)	LHMDS (equiv)	yield (%)
0.95	0.143	68
1.05	0.143	4
0.95	0.158	68
1.05	0.158	70
0.90	0.165	66

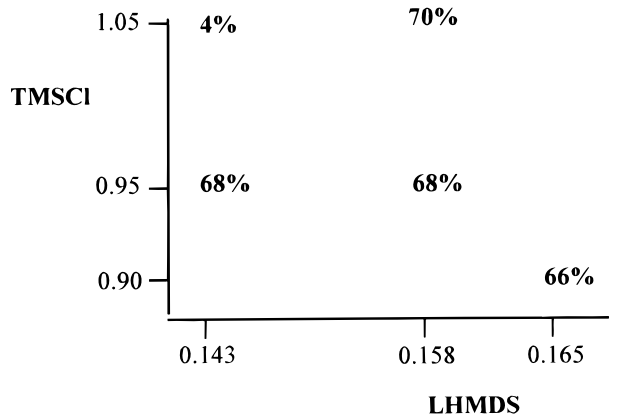


Figure 6. **Plot of the data from the extended 2^2 factorial design (Table 7).**

equiv of TBA and 0.15 equiv of LHMDS.

Next, the LHMDS (for the condensation) and TMSCl stoichiometries were varied in an extended 2^2 factorial design. Results of these experiments are shown in Table 7 and Figure 6. It was evident that, at high TMSCl levels and low LHMDS levels, the reaction failed. GC analysis again indicated that this was due to nonconsumption of the imine **3**. Presumably an excess of TMSCl quenched some of the available LHMDS, resulting in incomplete reaction. The TMSCl level was set at 0.95 equiv and the second LHMDS level at 0.1575 equiv for an initial piloting run.

Results

The stoichiometry for the LHMDS (for the condensation) was adjusted slightly to 0.19 equiv. The resulting process was subsequently operated successfully on a 200 gal scale, with the average yield being 70.2% over 25 batches (see Figure 7). With the exception of two batches, which fell slightly outside of the control limits, the process ran very reproducibly.

Conclusions

Utilizing statistical experimental design (DOE) and calorimetry as tools, a one-pot process for the preparation of an important β-amino acid ester was developed and implemented. This had significant advantages compared to a previous two-pot process. The new process operated at temperatures up to −20 °C compared to the −45 °C for the two-pot process. This enabled scaleup beyond the 50 gal vessels in our plant, and the one-pot process performed consistently over 25 batches run on a 200 gal scale. Apart from being able to operate at a higher temperature, the one-pot process used less LHMDS and required a smaller quench volume than the two-pot process. Accordingly, the new process had a 25% greater throughput, produced 15% less waste volume, and had a 3% higher average yield when compared to the two-pot process. In addition, implementation of the new process reduced the time required to produce chemical in the plant by 70% when compared to the two-pot process. The introduction of this technology enabled us to meet our short-term production requirements, and the process should be suitable for further scaleup.

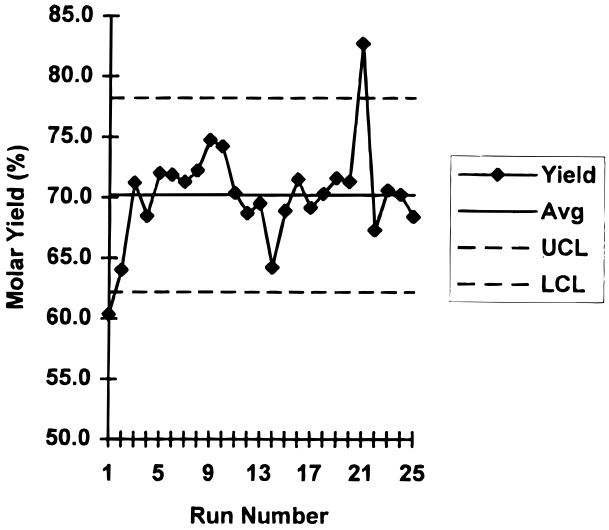


Figure 7. **Results of 25 batches of the one-pot process at the 200 gal scale. Average yield (Avg), upper control limit (UCL), and lower control limit (LCL) are shown.**

Experimental Section

The NMR spectra and microanalyses were obtained by our Physical Methodology Department. NMR spectra were recorded using a 400 MHz Varian VXR spectrometer.

Analytical GC was performed on a Hewlett-Packard 5890 instrument using an HP-1 column (10 m × 0.53 mm × 2.65 μm film thickness). The aldehyde **2** was obtained from the Aldrich Chemical Co. as a 50−60% solution in methyl *tert*-butyl ether (MTBE). This was quantitated by GC prior to use. All other reagents and solvents were obtained from commercial sources and used without further purification.

(±)-1,1-Dimethylethyl 3-Amino-5-(trimethylsilyl)-4-pentynoate (1).[20] A 200 gal reactor was charged with ammonium chloride (11.3 kg, 0.211 kmol) and water (64 L). The reactor was purged with nitrogen and stirred with a jacket temperature of 20−25 °C to dissolve the ammonium chloride. This was the quench solution.

A separate 200 gal reactor was dried under a sweep of dry nitrogen. LHMDS (245 kg = 275 L of a 1 M solution in THF, 0.275 kmol) was charged to the reactor using a vacuum. The addition line was rinsed with dry THF (3 L) using nitrogen pressure, and a sweep of nitrogen was put into place. The contents of the reactor were cooled to between −30 and −40 °C (jacket temperature −40 °C) with the agitator set at 77 rpm. 3-(Trimethylsilyl)-2-propynal (**2**) (55.1 kg of a 57.3% solution in MTBE, 0.250 kmol) was added over 1.25 h while the batch temperature was main-

(20) Babiak, K. A.; Babu, S.; Behling, J. R.; Boys, M. L.; Cain-Janicki, K. J.; Doubleday, W. W.; Farid, P.; Hagen, T. J.; Hallinan, E. A.; Hanson, D. W., Jr.; Korte, D. E.; McLaughlin, K. T.; Medich, J. R.; Nugent, S. T.; Orlovski, V.; Park, J. M.; Peterson, K. B.; Pilipauskas, D. R.; Pitzele, B. S.; Tsymbalov, S.; Stahl, G. L. US Patent 5536869, July 16, 1996.

tained at or below −20 °C (jacket temperature −45 °C). The addition line was rinsed with dry THF (3 L), and chlorotrimethylsilane (25.8 kg, 0.237 kmol) was immediately charged over 0.75 h while the batch temperature was maintained at or below −20 °C. Dry THF (3 L) was added to rinse the addition line, and *tert*-butyl acetate (174.4 kg, 1.50 kmol) was charged over 0.75 h while the batch temperature was maintained below −20 °C. The addition line was rinsed with dry THF (3 L), and the batch was cooled to between −30 and −40 °C. LHMDS (43.3 kg = 48.6 L of a 1 M solution in THF, 0.0486 kmol) was charged over 0.6 h while the batch temperature was maintained below −20 °C. The addition line was rinsed with dry THF (3 L), and the reaction mixture was transferred to the quench solution in the other 200 gal reactor via a flexible Teflon-lined transfer hose. THF (5 L) was used to rinse the transfer line. The mixture was warmed to 25 °C while being stirred at 77 rpm. The mixture was stirred for 1.25 h, agitation was stopped, and the phases were allowed to separate. The lower aqueous phase was transferred to a drum for disposal as waste. The organic phase was distilled under vacuum to remove the solvent (batch temperature < 35 °C). The distillate was disposed of as waste. The product remaining was (±)-1,1-dimethylethyl 3-amino-5-(trimethylsilyl)-4-pentynoate (**1**) (79.0 kg, which analyzed at 53.5% by weight using quantitative GC vs a pure reference standard). The net yield was (42.3 kg, 70 %).

The crude reaction material may be purified by crystallization of the 4-toluenesulfonic acid salt from heptane/MTBE (7:1). Liberation of the free amine with aqueous potassium carbonate and extraction into an organic solvent such as MTBE provides (following removal of solvent) pure **1**. Alternatively the material may be purified by distillation under vacuum. A sample of purified **1** analyzed as follows: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.96 (1H, dd, J = 8, 5 Hz), 2.60−2.47 (2H, m), 1.65 (2H, s, NH_2), 1.45 (9H, s), 0.15 (9H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.05, 107.96, 86.60, 80.85, 43.87, 41.02, 28.05 (3C), −0.13 (3C). Anal. Calcd for $C_{12}H_{23}NO_2Si$: C, 59.70; H, 9.60; N, 5.80. Found: C, 59.85; H, 9.67; N, 5.74.

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