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Development of a Scalable Process for 1-(3,5-Dichlorophenyl)-5-iodo-3-methyl-(4-methylbenzyl)-1*H*-imidazo[1,2-*a*]imidazol-2-one: A Key Intermediate for the Synthesis of LFA-1 Inhibitors

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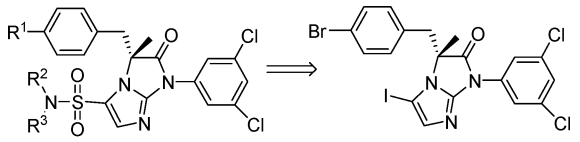
Abstract:

A safe, robust, chromatography-free and reproducible process for the multi-kilogram synthesis of vinyl iodide 2, a key intermediate for the synthesis of LFA-1 inhibitors, was developed and implemented at the pilot plant. Execution of the above process allowed us to support preclinical activities in the LFA-1 program.

Introduction

Small molecules that block the protein−protein interaction of cell adhesion molecules such as LFA-1 (lymphocyte function-associated antigen) and ICAM-1 (intracellular cell adhesion molecule) are potential drugs for the treatment of immune disorders such rheumatoid arthritis, psoriasis, and Crohn's disease.[1] Accordingly, SAR studies by our Discovery department aimed at identifying potent LFA-1 inhibitors led to the selection of 1*H*-imidazo[1,2-α]imidazol-2-ones such as **1** (Figure 1) as promising clinical candidates.[2] As a result, the need arose for the preparation of multi-kilogram quantities of these compounds in order to support preclinical activities. Since the original Discovery route suffered from a number of limitations that made it unsuitable for scale-up, process research was initiated to develop a suitable and scaleable synthetic route toward these compounds. A major drawback of the original route was the synthesis of intermediate **2** (Figure 1) by means of a nonregioselective iodination. Herein, we report the development of a scaleable process for the regioselective synthesis of key intermediate **2** for its multi-kilogram production in the pilot plant.



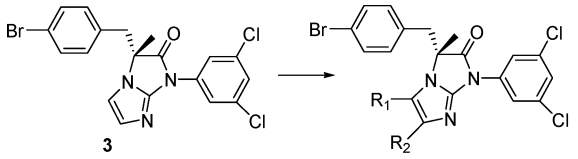
1, R^1 = Br, aryl or heterocycle
R^2 = H or alkyl
R^3 = H or alkyl

2

Figure 1.

Results and Discussion

As mentioned above, in the original Discovery route compound **2** was obtained by means of a nonregioselective iodination of **3** with NIS at ambient temperature. This iodination gave a 4:1 mixture of **2** and **5** (eq 1) that was



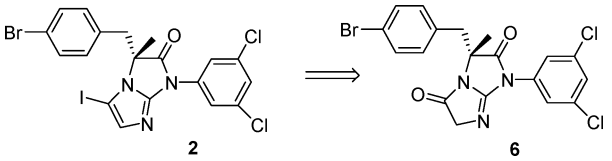
(1)

3

2, R^1 = I, R^2 = H
4, R^1 = H, R^2 = I
5, R^1 = I, R^2 = I

separated by silica gel chromatography. Evaluation of different reaction conditions failed to give **2** as a single product, but by reducing the temperature to 0 °C and quenching the reaction at 60% conversion, the ratio of **2** to **5** was improved to approximately 11:1 along with traces of **4** (3−5%). However, the isolation of **2** still required a difficult and labor intensive purification by silica gel chromatography.

To circumvent the regioselectivity problems associated with the direct iodination of **3**, we envisioned the synthesis of intermediate **6** (with the correct regiochemistry and the same oxidation state as **2**) and transformation of the lactam carbonyl group into the required vinyl iodide (Figure 2).



2 **6**

Figure 2.

Bis-lactam **6** was prepared from **7**[3] according to our previously described synthesis (Scheme 1).[4] Dehydration reagents other than Ph_3P/CCl_4, such as Burgess reagent or *p*-TsCl/Et_3N, failed to give any of the desired **8**.

With a practical route to intermediate **6** now established, we turned our attention to the transformation of bis-lactam **6** into iodide **2**. Early attempts at implementing Wiemer's[5] procedure for the TMSI (or TMSCl/NaI) promoted trans-

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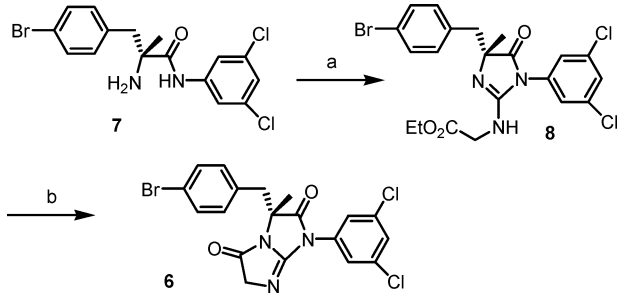
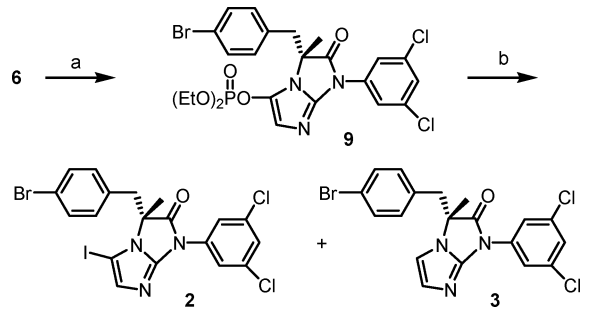
Scheme 1[a]



[a] Reagents and conditions: (a) (i) Ethyl isocyanoacetate, CH_2Cl_2, rt, 2.5 hr; (ii) Ph_3P, CCl_4, Et_3N, rt, 12 h (81%); (b) Me_3Al, Ph_3PO, toulene, 25 °C (91%).

Scheme 2[a]



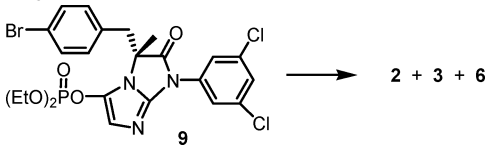
[a] Reagents and conditions: (a) $KN(TMS)_2$, $(EtO)_2POCl$, THF, −20 °C (92%); (b) NaI, TMSCl, H_2O, CH_2Cl_2 (70−75%).

formation of ketone-derived vinyl phosphates into vinyl iodides to our lactam-derived phosphate **9** resulted in low and irreproducible yields of **2**. After careful experimentation, however, we discovered that addition of 1 equiv of water to the reaction mixture resulted in good and consistent yields of iodide **2**.[4] Accordingly, vinyl iodide **2** was synthesized reproducibly in multi-kilogram amounts using the approach shown in Scheme 2.[6]

Our original[4] experimental conditions for the transformation of **9** into **2** involved addition of TMSCl (3 equiv), NaI (3 equiv), and water (1 equiv) to a solution of phosphate **9** in dichloromethane to give an approximately 6:1:1 mixture of **2**, **3**, and unreacted **9** along with traces of **6** after 2−5 h, resulting in a 70−75% isolated yield of **2** after chromatography (Table 1, entry 1). Prolonged reaction times resulted in larger amounts of **3**, and stopping the reaction earlier minimized the amount of **3** but resulted in a larger amount of unreacted **9**. In addition, under apparently identical reaction conditions, the time it took for the reaction to reach the desired product distribution varied considerably. As a result, the reaction had to be monitored closely by either HPLC or TLC and quenched at the optimum time to give the above-mentioned ratio of products.

To our knowledge there are no published reports on the mechanism for this transformation that could shed light into further improvement of this process. There were a few issues that needed to be investigated in order to improve the

Table 1. **Synthesis of 2 under different conditions**



entry	reagents and solvent	*T* (°C)	time	product ratios (**2:3:6:9**)	% yield (of **2**)
1	TMSCl (3 equiv) NaI (3 equiv) H_2O (0.7−1 equiv) CH_2Cl_2	25	2−5 h	75:12:<1:1	70−75
2	TMSCl (4 equiv) NaI (4 equiv) H_2O (2 equiv) CH_2Cl_2	25	20 min	75:12:<1:1	70−75
3	TMSCl (6 equiv) NaI (4.5 equiv) H_2O (4.5 equiv) CH_3CN	−15	80 h	90:5:3:2	82
4	TMSI (4.4 equiv) H_2O (2.9 equiv) CH_3CN	−7	40 h	86:5:1:8	82

efficiency of the reaction. For example, it was not obvious why the reaction required water to proceed efficiently, and the means by which compound **3** formed during the reaction were not clear. Moreover, the reaction mixture turned red/brown suggesting the formation of I_2, which was quenched upon addition of sodium thiosolfate. These issues needed to be understood better to facilitate the identification of the best possible reaction conditions that would maximize the yield of the desired product **2** and eliminate side product formation.

Reports on the use of the TMSCl/NaI/water system for the synthesis of vinyl iodides via hydroiodination of alkynes suggest this system is a good way to generate HI in situ under mild conditions.[7] Consequently, a possible mechanism for the transformation of **9** into **2** consistent with our observations and previous reports on the use of the TMSCl/NaI/H_2O system for the generation of HI is shown in Scheme 3. Accordingly, protonation of **9** followed by iodide addition to the resulting cation **10** would result in **11**, which upon elimination of diethyl phosphate would afford the desired vinyl iodide **2**. In the presence of excess HI under prolonged reaction times, however, iodide **2** could be protonated to give **12**, which would result in the formation of **3** upon elimination of I_2.

In agreement with the proposed mechanism is the observation that a significant amount of the proto-deiodination side product **3** is obtained when iodide **2** is resubmitted to the reaction conditions. Furthermore, when D_2O is added to the reaction mixture instead of H_2O, **3** is obtained with deuterium incorporation at the position formerly occupied by the iodide atom (eq 2).

With the above mechanism in mind, we looked at systematically modifying the reaction parameters (solvent, reaction time, temperature, order of addition, etc.) in order

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(6) Alternative procedures for the multi-kilogram production of **6** have been developed. For additional information on the subject, see Wang, X.-j.; Zhang, L.; Xu, Y.; Krishamurthy, D.; Varsolona, R.; Nummy, L.; Frutos, R. P.; Byrne, D.; Chung, J. C.; Farina, V.; Senanayake, C. *Tetrahedron Lett*. **2005**, *46*, 273.
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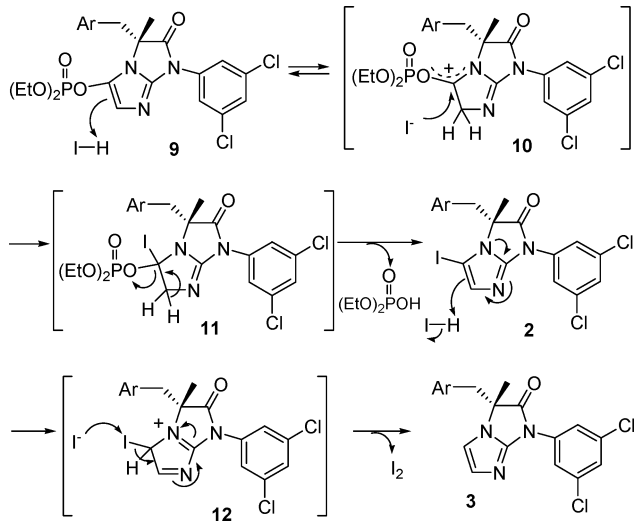
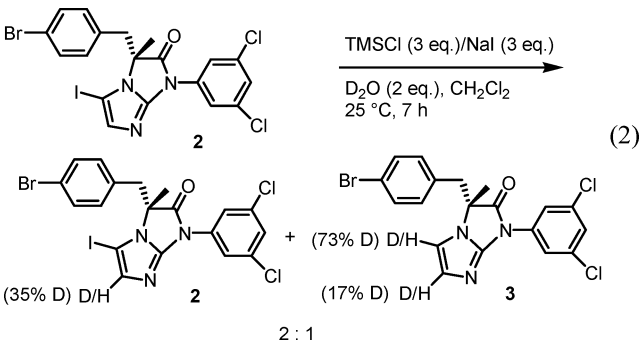
Scheme 3. **Proposed mechanism for the formation of 2 and 3 from 9**



to drive the reaction to completion, minimize the formation of **3**, eliminate the need for chromatography, and make the reaction conditions more suitable for pilot-plant implementation. Along these lines, some improvements were obtained by reversing the order of addition and charging a dichloromethane solution of phosphate **9** into a premade mixture of TMSCl and NaI in dichloromethane. Also, the amounts of TMSCl and NaI were increased to 4 equiv as opposed to 3, and the amount of water was increased to 2 equiv relative to **9**. In addition, powdered NaI was utilized to minimize solubility issues associated with particle size. Under these modified conditions, the yield and product distribution did not change significantly, but the time it took for the reaction to reach the above product distribution was consistent (Table 1, entry 2). However, the reaction was much faster and had to be quenched after approximately 20 min at ambient temperature to avoid excessive formation of **3**. As a result, it was difficult to monitor the reaction progress, but the reaction time, product ratios, and yield were reproducible, permitting the implementation of these conditions in fixed equipment at the pilot plant for the synthesis of multi-kilogram amounts of **2**.



We also investigated the use of commercially available aqueous solutions of HI; however, the use of these solutions gave poor results resulting in the formation of mostly unreacted **9** and lactam **6**, which most likely forms from the hydrolysis of **9**.

Ultimately, major improvements were realized by lowering the reaction temperature and changing the solvent from dichloromethane to acetonitrile. Under the improved conditions, the HI catalyzed proto-deiodination pathway of **2** to **3** was minimized and **2** was obtained in a higher yield and with an improved impurity profile. Accordingly, using the TMSCl/NaI system in acetonitrile at −15 °C (Table 1, entry 3), the formation of **2** was more favorable although the reaction took a long time to reach completion. However, the reaction time could be shortened by using commercially available TMSI (4.4 equiv) instead of NaI/TMSCl to overcome the poor solubility of NaI and accelerate the reaction (Table 1, entry 4). Also, the amount of water was adjusted (2.8 equiv) once again to maximize the yield and minimize the formation of impurities. Hence, although the reaction still took a considerably long time to reach completion (40 h), it was reproducible and robust. Accordingly, under the above conditions the **2:3:9:6** product distribution was a much improved 86:5:1:8. Most importantly, the improved impurity profile of the reaction now allowed for the isolation of iodide **2** by crystallization in 82% yield and >98% purity eliminating the need for silica gel chromatography. This third generation process was then successfully implemented at our pilot plant for the synthesis of multi-kilogram amounts of **2**.

Conclusion

To summarize, based on our proposed mechanism for the formation of **2** from **9** (Scheme 3), we developed a safe, robust, chromatography-free, and reproducible process for the multi-kilogram synthesis of vinyl iodide **2** at the pilot plant. Implementation of the above process allowed us to support the drug substance needs of toxicology and formulation in the LFA-1 program.

Experimental Section

Unless otherwise specified, all reactions were carried out in oven-dried glassware under an atmosphere of nitrogen. NMR spectra were recorded on a Bruker DPX-400 NMR spectrometer. Shifts are reported in ppm relative to trimethylsilane; coupling constants (*J*) are reported in hertz, refer to apparent peak multiplicities, and may not necessarily be true coupling constants. The commercially available starting materials were used as received without further purification, and all solvents were dried by standard methods prior to use. All melting points are recorded using a Fisher−Johns melting point apparatus and are uncorrected.

3-(4-Bromobenzyl)-1-(3,5-dichlorophenyl)-5-iodo-3-methyl-1*H*-imidazo[1,2-a]imidazol-2-one (2): Phosphate **9** (45.7 g. 78.7 mmol), MeCN (240 mL), and water (3.97 mL, 221 mmol) were charged sequentially into a 1 L flask, and the solution was cooled to −15 °C. TMSI (49.3 mL, 347 mmol) was added slowly over 30 min maintaining the internal temperature below −7 °C. The resulting yellow suspension was stirred for 40 h. The mixture was diluted with toluene (125 mL) maintaining the temperature at −7 °C, and the resulting cold suspension was quenched with 5 M NaOH (63 mL). The organic layer was concentrated by

distillation, and additional toluene (315 mL) was charged followed by aqueous 0.5 M Na_2SO_3 (188 mL). The aqueous layer was discarded, and the organic layer was washed with aqueous 2% NaCl (250 mL). The toluene solution was filtered through a pad of layered Celite 545 (26 g), silica gel 60 (83 g) and active carbon (Darco G-60, 10.2 g), and the cake washed with additional toluene (2 × 125 mL). The combined toluene layer was concentrated under reduced pressure to an oil and azeotroped with IPA (2 × 125 mL) to remove residual toluene. The residue was heated to 75 °C and diluted with IPA (70 mL) to afford a 34% w/w solution of **2**. The solution was cooled to room temperature (4 °C/hour), diluted with water (38 mL), and stirred for 2 h. The solid product was collected by filtration, washed with 40% w/w aqueous 2-propanol, and dried to afford 37.3 g of **2** (82%) as an off-white solid (>95% purity). ^{1}H NMR: δ 7.54 (d, J = 1.8, 2H), 7.24−7.29 (m, 3H), 6.96 (s, 1H), 6.78 (d, J = 8.4, 2H), 3.53 (d, J = 14, 1H), 3.24 (d, J = 14, 1H), 1.92 (s, 3H). ^{13}C NMR: δ 174.3, 148.8, 135.8, 135.4, 134.2, 132.0, 131.8, 131.0, 127.4, 122.2, 120.6, 68.4, 56.7, 42.0, 22.2. HRMS (APCI): calcd for $C_{19}H_{14}N_3OCl_2BrI$, 575.8736; found, 575.8742.

3-(4-Bromobenzyl)-1-(3,5-dichlorophenyl)-3-methyl-1,6-dehydro-imidazo[1,2-a]imidazole-2,5-dione (6): Method A: Toluene (450 mL) was added to 76.9 g of a mixture of ester **8** (47.1 g, 91.7 mmol) and triphenylphosphine oxide (29.2 g, 105 mmol), and the resulting solution was cooled to −10 °C. Trimethylaluminum (46 mL of a 2 M solution in toluene, 92 mmol) was added dropwise keeping the temperature at or below 0 °C, and the mixture was then allowed to reach ambient temperature. The mixture was stirred at ambient temperature for 2 h, and more trimethylaluminum (27.6 mL of a 2 M solution in toluene, 55.2 mmol) was added in two portions at 2 h intervals. The mixture was placed over an ice bath and slowly quenched with 1 N HCl (360 mL). The organic portion was separated, and the aqueous portion was extracted with toluene (200 mL). The combined organic portions were washed with water and concentrated under reduced pressure to afford an orange oil. Flash chromatography (silica gel, hexanes/ethyl acetete 4:1 v/v) afforded 38.1 g (89%) of product as an oil that solidified upon standing: mp 52−54 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84 (s, 3H), 3.24 (d, J = 13.8 Hz, 1H), 3.43 (d, J = 13.8 Hz, 1H), 4.18 (d, J = 21.9 Hz, 1H), 4.30 (d, J = 21.9 Hz, 1H), 6.95 (d, J = 8.3 Hz, 2 H), 7.29 (d, J = 1.8 Hz, 2H), 7.33 (t, J = 1.8 Hz, 1H), 7.38 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 40.8, 61.3, 65.1, 122.3, 122.6, 128.5, 131.0, 132.0, 132.5, 132.7, 135.5, 154.6, 174.3, 174.9. Anal. Calcd for $C_{19}H_{14}BrC_{l2}N_3O_2$: C, 48.85; H, 3.02; N, 9.00. Found: C, 48.89; H, 3.02; N, 8.81. HRMS (APCI): calcd for $C_{19}H_{15}N_3O_2Cl_2Br$, 465.9719; found, 467.9703.

[4-(4-Bromobenzyl)-1-(3,5-dichlorophenyl)-4-methyl-5-oxo-imidazolidin-2-ylideneamino]acetic Acid Ethyl Ester (8): Ethyl isocyanatoacetate (0.287 mL, 2.56 mmol) was added dropwise to a stirred solution of **7** (1.0 g, 2.49 mmol) and dichloromethane (5 mL) at room temperature. The mixture was stirred for 10 min at room temperature, and the urea intermediate formed as a white precipitate. Triphenylphosphine (1.31 g, 4.98 mmol), triethylamine (0.69 mL, 4.98 mmol), and carbon tetrachloride (0.48 mL, 4.98 mmol) were added to the stirred suspension. The mixture was then stirred at ambient temperature for 12 h. Aqueous workup (1 N HCl, dichloromethane, $MgSO_4$) afforded a yellow oil. Flash chromatography (silica gel, 4:1 hexanes/ethyl acetate v/v) afforded 906 mg (71%) of product as a white solid: mp 103−105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (t, J = 7.1 Hz, 3H), 1.52 (s, 3H), 2.95 (d, J = 12.9 Hz, 1H), 2.98 (d, J = 12.9 Hz, 1H), 4.05−4.13 (m, 3H), 4.23 (m, 2H), 6.57 (d, J = 1.6 Hz, 2H), 7.04 (d, J = 8.2 Hz, 2H), 7.37 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 23.7, 42.9, 44.2, 61.7, 70.4, 120.9, 125.6, 129.4, 130.8, 131.9, 133.2, 134.8, 136.1, 151.1, 169.6, 181.5. Anal. Calcd for $C_{21}H_{20}BrCl_2N_3O_3$: C, 49.15; H, 3.93; N, 8.19. Found: C, 49.46; H, 3.92; N, 7.96.

Phosphoric Acid 5-(4-Bromobenzyl)-7-(3,5-dichlorophenyl)-5-methyl-6-oxo-6,7-dihydro-5*H*-imidazo[1,2-a]-imidazol-3-yl Ester Diethyl Ester (9): Potassium bis-(trimethylsilyl)amide (265 mL of a 0.5 M solution in toluene, 133 mmol) was added dropwise to a stirred solution of **6** (51.5 g, 110.3 mmol) and diethyl chlorophosphate (23.9 mL, 165 mmol) at −20 °C. The mixture was stirred at −20 °C for 1 h. Aqueous workup (aqueous NH_4Cl, ethyl acetate, $MgSO_4$) afforded an oil. Flash chromatography (silica gel, hexanes/ethyl acetate 2:1 v/v) afforded 61.2 g (92%) of product **9** as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (t, J = 7.1 Hz, 6H), 1.86 (s, 3H), 3.26 (d, J = 13.9 Hz), 3.34 (d, J = 13.9 Hz, 1H), 4.33 (m, 4 H), 6.50 (s, 1H), 6.84 (d, J = 8.2 Hz, 2H), 7.24−7.28 (m, 3H), 7.58 (d, J = 1.6 Hz, 2H).

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