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Efficient Synthesis of a Small Molecule, Nonpeptide Inhibitor of LFA-1

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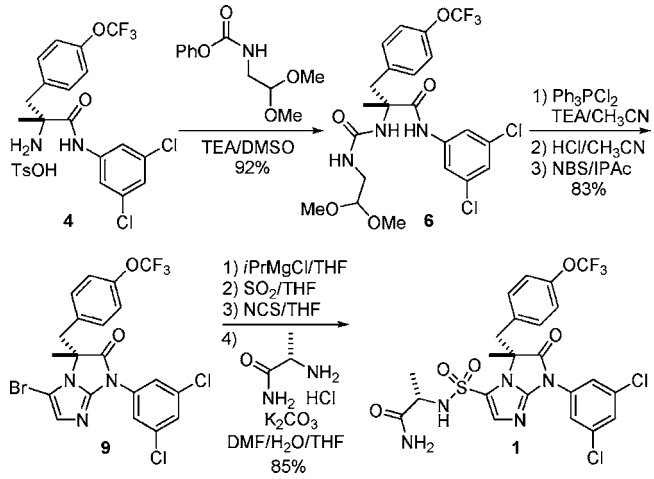
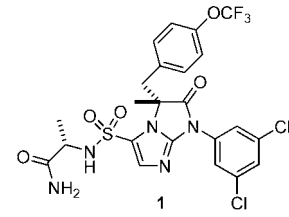
ABSTRACT



A three-stage process for the synthesis of LFA-1 inhibitor 1 from amine 4 with an overall yield of 65% is described. The key stage involves a Ph_3PCl_2-induced dehydration/cyclization of urea 6 followed by a regioselective bromination to give 1*H*-imidazo[1,2-*a*]imidazol-2-one 9. Br/Mg exchange of 9 followed by addition to SO_2 in THF and subsequent oxidation produces a sulfonyl chloride which is directly reacted with L-alaninamide using K_2CO_3 as base in aqueous DMF/THF to give 1 in a one-pot operation. The process was implemented for the production of 1 on a metric ton scale.

Recently, we described a series of novel and potent 1*H*-imidazo[1,2-*a*]imidazol-2-ones such as compound **1** as the first small molecule, nonpeptidic inhibitors of lymphocyte function-associated antigen **1**.[1] These LFA-1 antagonists have potential therapeutic application for treatment of inflammatory and immune disorders, and we were interested in developing an efficient process for **1** on production scale.

We previously reported a first-generation process for the synthesis of analogous LFA-1 inhibitors in which a CuCl-promoted cyclization of thiourea **A** established the bicyclic core **B** which was then transformed to 1*H*-imidazo[1,2-*a*]imidazol-2-one derivatives through multiple steps (Scheme 1).[2] The use of stoichiometric CuCl and the long linear sequence made this process less efficient and cost-effective. A more robust and efficient synthesis was necessary to satisfy the need for metric ton production of **1**.



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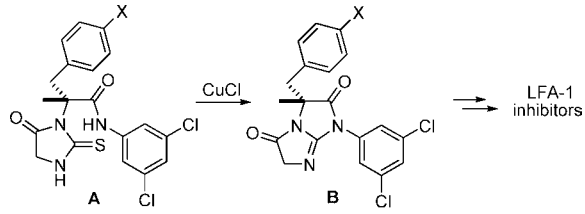
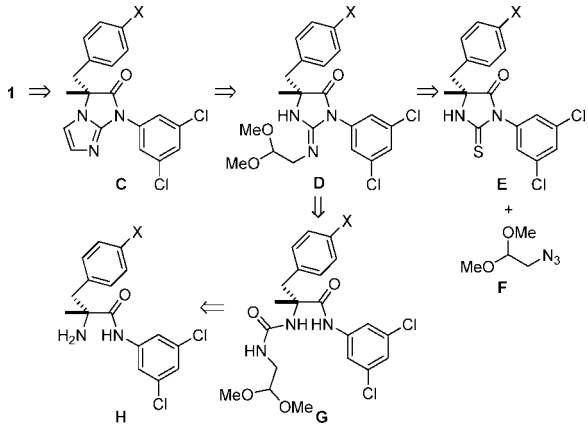
Scheme 1. First-Generation Process for LFA-1 Inhibitors



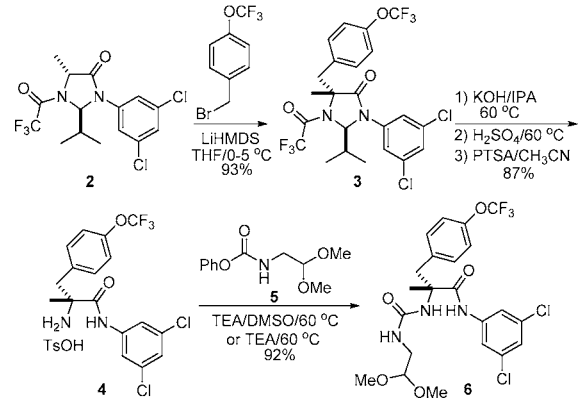
Retrosynthetically (Scheme 2), compound **1** and its analogues can be disconnected to the key bicyclic imidazole **C** which is readily derived from guanidine **D** bearing a protected aldehyde function. In the original discovery route, **D** was prepared from the condensation of thiohydantoin **E** and a potentially explosive azide **F**. We envisioned that a urea such as **G** could be dehydrated and cyclize to **D**, presumably through a transient carbodiimide intermediate.[2b] Urea **G** is readily accessible from **H**.

Scheme 2. Retrosynthetic Analysis of Analogous **1**



The synthesis of chiral amine **4** (which is analogous to intermediate H in the retrosynthetic scheme) began with template **2** which was prepared using a process based on Seebach's principle of self-regeneration of stereocenters (Scheme 3).[3] A highly diastereoselective alkylation, performed by addition of $LiN(TMS)_2$ to a mixture of **2** and

Scheme 3. Synthesis of Urea **6** Bearing a Protected Aldehyde Function



p-trifluoromethoxybenzyl bromide in THF at 0−5 °C, gave compound **3** in 93% isolated yield. Cleavage of the protecting groups was conducted in one-pot by the successive treatment of **3** with KOH in IPA at 60 °C followed by 3 M sulfuric acid. Chiral amine **4**, as the PTSA salt, was isolated in 87% yield by crystallization from acetonitrile. Coupling of **4** with phenylcarbamate **5**[4] in the presence of TEA in DMSO at 60 °C gave urea **6** in 92% yield after crystallization from methanol.[5] While other solvents such as MeOH or CH_3CN significantly slowed the reaction which was in agreement with the literature report,[5] a similar result was achieved using TEA to replace DMSO as solvent. With the urea **6** in hand, we next studied the dehydration/cyclization to **7**, a central strategy for the establishment of the 1*H*-imidazo[1,2-*a*]imidazol-2-one system.

We initiated the dehydration/cyclization of urea **6** using a combination of Ph_3P, CCl_4, and TEA,[6] which was proven to be effective in the synthesis of a similar guanidine derivative.[2b] The reaction indeed produced **7** (as a 1:1 mixture of two endo- and exoisomers) in 94% isolated yield. However, the use of toxic CCl_4 as reagent was a drawback for this reaction. A literature search revealed that the combination of Ph_3P and CCl_4 was sometimes used for the preparation of Ph_3PCl_2 which is now commercially available, inexpensive, and often used for *N*-ylide formation.[7] Having this information, we studied the possibility of applying this reagent for our dehydration reaction. We were pleased to find that treatment of a mixture of **6** and 3.5 equiv of TEA in acetonitrile with 1.7 equiv of moisture-sensitive Ph_3PCl_2

(1) (a) Wu, J.-P.; Emeigh, J.; Gao, D. A.; Goldberg, D. R.; Kuzmich, D.; Miao, C.; Potocki, I.; Gian, K. C.; Sorcek, R. J.; Jeanfavre, D. D.; Kishimoto, K.; Mainolfi, E. A.; Nabozny, G., Jr.; Peng, C.; Reilly, P.; Rothlein, R.; Sellati, R. H.; Woska, J. R., Jr.; Chen, S.; Gunn, J. A.; O'Brien, D.; Norris, S. H.; Kelly, T. A. *J. Med. Chem.* **2004**, *47*, 5356–5366. (b) Last-Barney, K.; Davidson, W.; Cardozo, M.; Frye, L. L.; Grygon, C. A.; Hopkins, J. L.; Jeanfavre, D. D.; Pav, S.; Qian, C.; Stevnson, J. M.; Tong, L.; Zindell, R.; Kelly, T. A. *J. Am. Chem. Soc.* **2001**, *123*, 5643–5650. (c) Kelly, T. A.; Jeanfavre, D. D.; McNeil, D. W.; Woska, J. R., Jr.; Reilly, P. L.; Mainolfi, E. A.; Kishimoto, K. M.; Nabozny, G. H., Jr.; Zinter, R.; Bormann, B.-J.; Rothlein, R. J. *Immunology* **1999**, *163*, 5173–5177.

(2) (a) Wang, X.-j.; Zhang, L.; Xu, Y.; Krishnamurthy, D.; Varsolona, R.; Nummy, L.; Shen, S.; Frutos, R. P.; Byrne, D.; Chung, J. C.; Farina, V.; Senanayake, C. H. *Tetrahedron Lett.* **2005**, *46*, 273–276. (b) Frutos, R. P.; Johnson, M. *Tetrahedron Lett.* **2003**, *44*, 6509–6511.

(3) (a) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2708–2748. (b) Frutos, R. P.; Stehle, S.; Nummy, L.; Yee, N. *Tetrahedron: Asymmetry* **2001**, *12*, 101–104. (c) Yee, N. K. *Org. Lett.* **2000**, *2*, 2781–2783.

(4) Carbamate **5** was prepared by the reaction between aminoacetyaldehyde dimethyl acetal and phenyl chloroformate in the presence of TEA in MTBE. After filtration to remove TEA HCl salt, the concentrated solution (can be stored) was used directly.

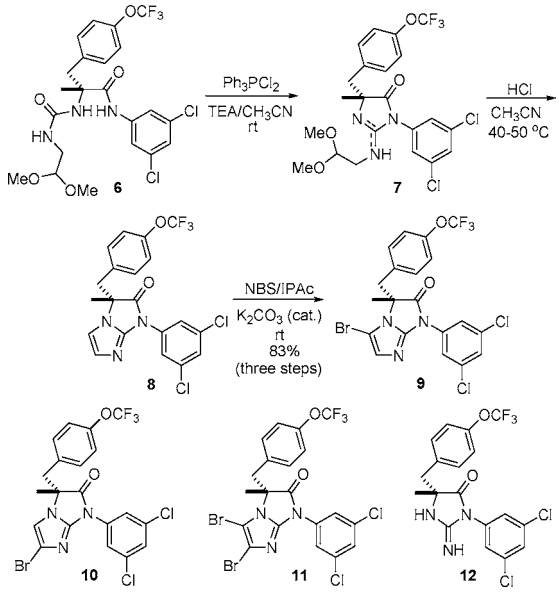
(5) Thavonekham, B. *Synthesis* **1997**, 1189–1194.

(6) Appel, R.; Kleinstuck, R.; Ziehn, K. *Chem. Ber.* **1971**, *104*, 1335–1336.

(7) (a) Wamhoff, H.; Schupp, W.; Kirfel, A.; Will, G. *J. Org. Chem.* **1986**, *51*, 149–154. (b) Wamhoff, H.; Haffmanns, G.; Schmidt, H. *Chem. Ber.* **1983**, *116*, 1691–1707.

in acetonitrile, by a slow addition at 20−25 °C, gave **7** in quantitative yield (Scheme 4). Without a workup, the resulting mixture was immediately subjected to treatment with concentrated HCl at 40−50 °C, and bicyclic imidazole **8** was obtained in 95% isolated yield over two steps by chromatographic purification. Since **8** purified through silica gel column was still an oily compound, after a simple aqueous workup the IPAc solution[8] of crude **8** containing Ph_3PO was directly used for the subsequent halogenation and sulfonylation to **1**.

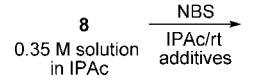
Scheme 4. Ph_3PCl_2-Induced Dehydration/Cyclization of **6** and Subsequent Bromination of Imidazole **8** to **9**



Functionalization of **8** by both iodination and bromination was examined. The expensive NIS with a catalytic amount of PPTS produced the iodo derivative with the best conversion and chemoselectivity. About 10% of the diiodide analogous to **11** (Scheme 4) was formed.[1a] The removal of this byproduct from the desired monoiodide (analogous to **9**) by crystallization was difficult without a large decrease in the isolated yield of the desired isomer. Bromination of **8** was expected to avoid these issues considering the fact that bromination of *N*-alkylimidazoles,[9] imidazo[1,2-*a*]pyrimidines[10] and imidazo[1,2-*a*]pyridine derivatives[11] is very regio- and chemoselective.

Bromination of **8** was investigated directly with the IPAc solution coming from the previous step which would greatly simplify the process. Table 1 outlines the results of some typical experiments.

Table 1. Bromination of **8** with NBS to Bromoimidazole **9**



entry	additive (0.1 equiv)	dimerization derivatives (area, %)[a]	time (h)	isolated yield of **9**[b] (%)
1		11	1	63
2[c]		11	1	64
3	PPTS	13	1	58
4	$ZnBr_2$	22	0.5	45
5	TEA	2	1	83
6	K_2CO_3	1	1	86

[a] Area % by HPLC of the reaction mixture. [b] Crystallization from a mixture of IPA/water. [c] Purified **8** used.

A treatment of **8** by slow addition of a suspension of 1.05 equiv of NBS in IPAc produced bromoimidazole **9** in 57% yield with only a trace amount of regioisomer **10** and <2% of dibromide **11**. A similar result was obtained when purified **8** was used under the same conditions (entry 2, Table 1). Whereas the regio- and chemoselectivity were promising, bromide **9** was obtained only in moderate yield because several byproduct were observed in a combined yield of >10%. Isolation and identification of these byproduct was unsuccessful since they rapidly interconverted. On the basis of preliminary MS data, these byproducts are possibly products of imidazole dimerization.[12] Interestingly, in the presence of Lewis acids such as PPTS and $ZnBr_2$ for the bromination, formation of these byproduct significantly increased up to 22% (entries 3 and 4, Table 1). These experiments suggested that the proposed dimerization of **8** may be promoted by acids, and there are literature reports of Lewis acid promoted dimerization of imidazole-related heterocycles.[13] As expected, the same bromination of **8** in the presence of TEA significantly suppressed the formation of dimer derivatives (entry 5, Table 1), leading to a much improved 83% yield of **9**. In this case, about 1.4 equiv of NBS was needed for a complete reaction due to the reaction between TEA and NBS.[14] Subsequently, inorganic base K_2CO_3 was used to replace TEA, and indeed, the bromination of **8** produced **9** in 86% isolated yield with no need of excess NBS. Ph_3PO brought in from the previous step was fully removed by the same crystallization from IPA/water. In one instance, the bromination of crude **8** in IPAc gave only 40% of **9** due to the formation of a byproduct identified as **12**. An investigation revealed that an insufficient azeotropic

(8) Amounts of **8** in many batches of IPAc solutions, measured by weight % HPLC assay, were consistentally corresponding to about 95% yield from **6** over two steps. Therefore, halogenation reagents were charged based on this number.

(9) For examples, see: (a) Choshi, T.; Yamada, S.; Sugino, E.; Kuwada, T.; Hibino, S. *J. Org. Chem.* **1995**, *60*, 5899–5904. (b) Matthews, H. R.; Rapoport, H. *J. Am. Chem. Soc.* **1973**, *95*, 2297–2303. (c) Takeuchi, T.; Yeh, H. J. C.; Kirk, K. L.; Cohen, L. A. *J. Org. Chem.* **1978**, *43*, 3565–3570.

(10) For examples, see: (a) Jensen, M. S.; Hoerrner, R. S.; Li, W.; Nelson, D. P.; Javadi, G. J.; Dormer, P. G.; Cai, D.; Larsen, R. D. *J. Org. Chem.* **2005**, *70*, 6034–6039. (b) Rival, Y.; Grassy, G.; Michel, G. *Chem. Pharm. Bull.* **1992**, *40*, 1170–1176.

(11) For examplex, see: (a) Hua, D. H.; Zhang, F.; Chen, J. *J. Org. Chem.* **1994**, *59*, 5084–5087. (b) Knölker, H.-J.; Hitzemann, R. *Tetrahedron Lett.* **1994**, *35*, 2157–2160.

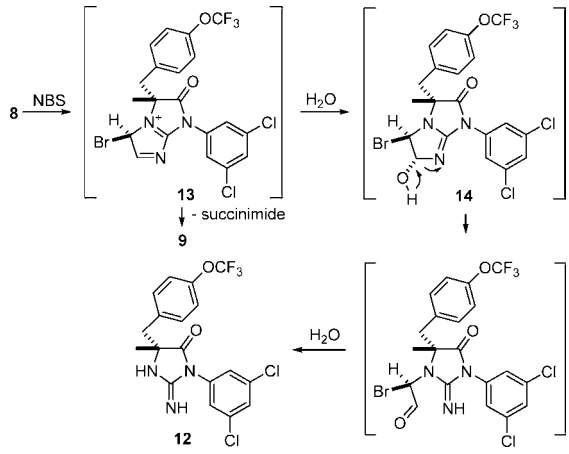
(12) On the basis of MS data, they are possibly hydrates of imidazole dimerization. The ring strain of dimers may lead to the addition of water.

(13) (a) Monguchi, D.; Yamamura, A.; Fujiwara, T.; Somete, T.; Mori, A. *Tetrahedron Lett.* **2010**, *51*, 850–852. (b) Stachel, S. L.; Habeeb, R. L.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1996**, *118*, 1225–1226.

(14) Dunstan, S.; Henbest, H. B. *J. Chem. Soc.* **1957**, 4905–4908.

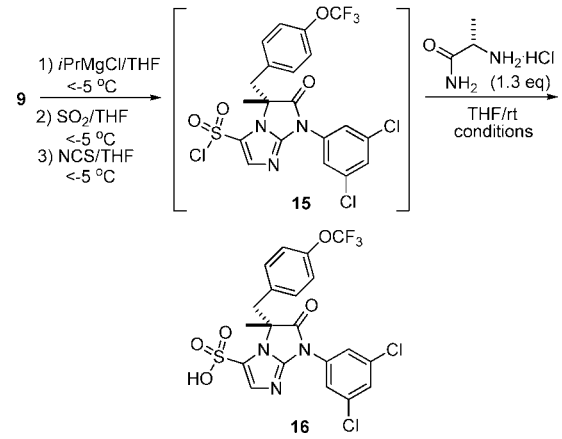
distillation of the IPAc solution of **8** after an aqueous workup led to the cleavage of the imidazole ring by NBS/water as rationalized in Scheme 5.

Scheme 5. Proposed Cleavage of Bicyclic Imidazole **8** to **12** with NBS in the Presence of Water



The final stage of the elaboration of **9** to **1** followed a process that had been previously applied to the synthesis of LFA-1 inhibitors.[1a,2] Br/Mg exchange of **9** was performed by addition of *i*-PrMgCl (1.05 equiv) in THF at <−5 °C. Upon completion of the charge of *i*-PrMgCl, successive addition of SO_2 (1.1 equiv) as a THF solution and a suspension of NCS (1.1 equiv) in THF to the reaction mixture at <−5 °C produced sulfonyl chloride **15**. Without workup, coupling of **15** with L-alaninamide was carried out. A screening of conditions revealed that the choices of solvents and bases had a significant impact on the reaction as shown in Table 2. Without a cosolvent, the coupling of **15** with L-alaninamide in the presence of TEA was sluggish, probably due to the poor reactivity and solubility of L-alaninamide in THF (entry 1). Addition of a mixture of L-alaninamide and TEA or pyridine in DMF (as cosolvent) to the reaction mixture of **15** produced **1** in only 40−50% yield due to the formation of a large amount of sulfonic acid **16** over the prolonged reaction time (entries 2 and 3). Inorganic base K_2CO_3 under the same conditions gave a similar result (entry 4). While the coupling reaction using a combination of DMF and water as cosolvent and TEA as base gave an improved yield of **1** (entry 5), the use of either K_2CO_3 and Cs_2CO_3 significantly reduced the formation of **16** with a complete reaction in 6 h resulting in 85−86% yield of **1** after crystallization from ethanol/water (entries 6−7). In the

Table 2. One-Pot Operation to LFA-1 Inhibitor **1** from **9**



entry	base[a]	cosolvent[b] (vol % to THF)[c]	time (h)	yield of **1**[d] (%) (wt % of **16**)[e]
1	TEA	/	20	<10
2	TEA	DMF (10)	17	45 (23)
3	py	DMF (10)	15	40 (25)
4	K_2CO_3	DMF (10)	20	51 (20)
5	TEA	DMF (10)/H_2O (10)	6	64 (13)
6	K_2CO_3	DMF (10)/H_2O (10)	6	85 (6)
7	Cs_2CO_3	DMF (10)/H_2O (10)	6	86 (5)
8	K_2CO_3	H_2O (10)	24	72 (11)

[a] 3 equiv for TEA and pyridine and 1.5 equiv for K_2CO_3 and Cs_2CO_3. [b] Added as L-alaninamide HCl salt solution. [c] Volume % to all THF used in the first three chemical transformations. [d] Isolated by crystallization from EtOH/water. [e] Weight % assay of the reaction mixture by HPLC.

absence of DMF, the reaction was drastically slowed down and 24 h was required for a complete reaction. Under these conditions, more hydrolysis of the sulfonyl chloride was observed (entry 8).

In summary, we have developed a concise, robust process for the production of LFA-1 inhibitor **1** on a metric ton scale. The synthesis features a new methodology for dehydration of urea with Ph_3PCl_2 and a regioselective bromination of imidazo[1,2-*a*]imidazol-2-one derivatives. Furthermore, an efficient one-pot process for the preparation of sulfonamide from bromoimidazole was also developed involving four chemical transformations.

Supporting Information Available: Experimental procedures, spectroscopic data, and copies of $^1H/^{13}C$ NMR spectra for **1**, **3**−**12**, **15**, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley-Interscience: Hoboken, NJ, 1992; pp 613−615.