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Tetrahedron Letters 46 (2005) 273–276
Tetrahedron Letters

A practical synthesis of LFA-1 inhibitors utilizing CuCl-promoted intramolecular cyclization of thiohydantoins

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Received 21 October 2004; accepted 10 November 2004

Abstract—An efficient and chromatography-free approach for synthesis of a new class of LFA-1 inhibitors was developed. A copper(I) chloride-promoted intramolecular cyclization of thiohydantoins **7a**–**b** serves as a key step to highly functionalized bicyclic guanidines **5a**–**b**, that were subsequently converted to 1*H*-imidazo[1,2-*a*]imidazol-2-one LFA-1 inhibitors. This process has been successfully implemented in the pilot plant to produce multikilogram quantities of LFA-1 inhibitors such as **1a**–**b**.

Our drug discovery program produced a series of 1*H*-imidazo[1,2-*a*]imidazol-2-ones such as compounds **1a**–**b** (Fig. 1) as the first small molecule, nonpeptidic inhibitors of LFA-1.[1–3] These LFA-1 antagonists have potential therapeutic application for treatment of inflammatory and immune disorders. However, synthesis of these highly functionalized fused bicyclic imidazoles with a quaternary stereocenter **1a**–**b**, **2a**–**b** and analogues remains a significant challenge to us with respect to scalability and efficiency of an approach to the key intermediates such as iodoimidazoles **2a**–**b**.

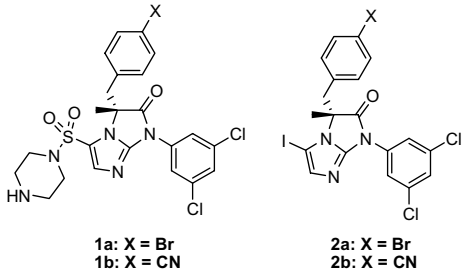
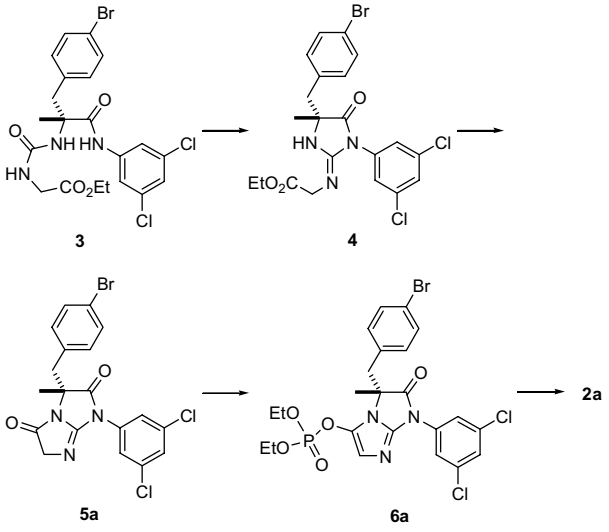


Figure 1.

A novel synthesis of iodoimidazole **2a** by a highly regio-controlled iodination of phosphate **6a** was reported (Scheme 1).[4] A key aspect of this route was dehydration of urea **3** with CCl_4/Ph_3P/TEA, followed by



Scheme 1.

Keywords: LFA-1 inhibitor; Bicyclic guanidine; Thiohydantoin; Imidazolidinone.
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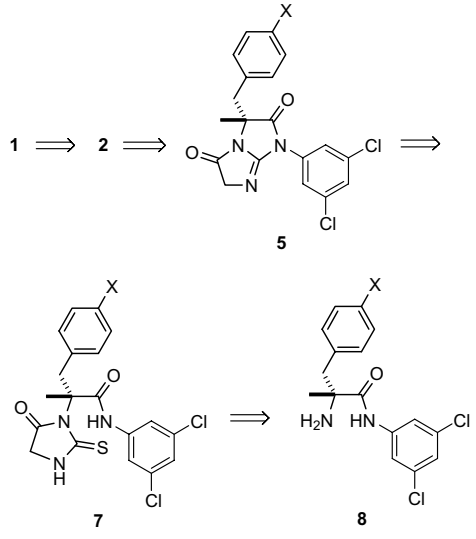
doi:10.1016/j.tetlet.2004.11.065

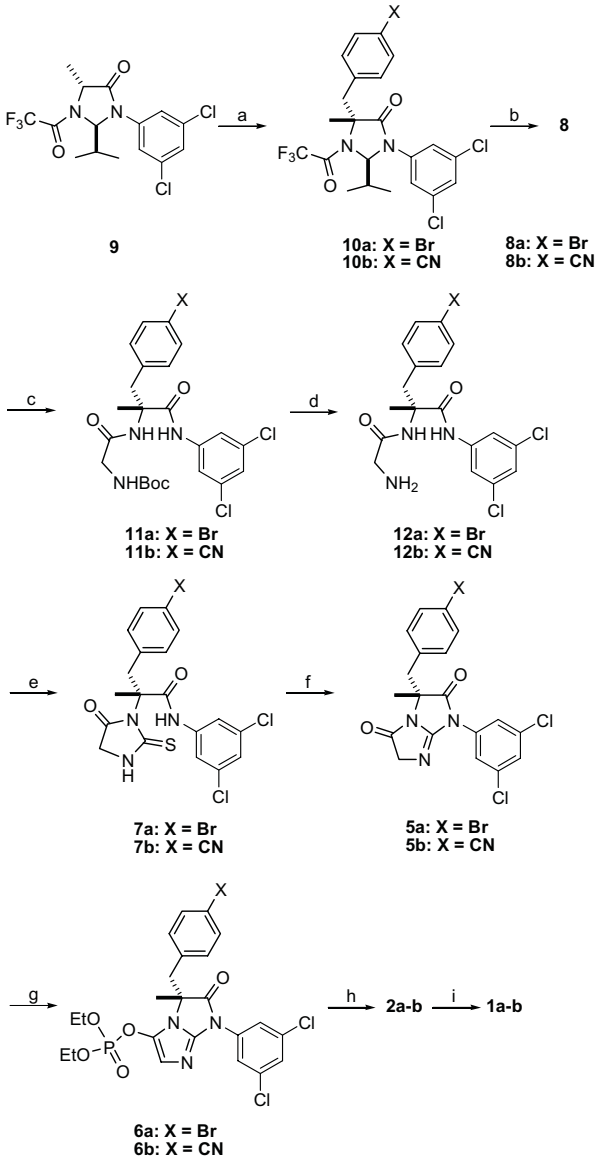
Me_3Al-mediated cyclization of guanidine derivative **4** to bicyclic guanidine **5a**. The use of a large excess triphenylphosphine resulted in a large amount of triphenylphosphine oxide, which was removed by impractical chromatography on silica gel. In addition, the use of highly toxic carbon tetrachloride was undesirable for large scale production. To circumvent these drawbacks of this approach and take advantage of the highly regio-controlled iodination of phosphate **6a** to **2a**, we decided to explore an alternative synthesis of bicyclic guanidine derivatives **5**.

Although compounds containing the guanidine unit are of considerable biological interest, there is a limited number of methods for the preparation of bicyclic guanidine derivatives.[5,6] We were particularly interested in Corey's synthesis of bicyclic guanidine by an intramolecular cyclization of thiourea using iodomethane.[6] In our retrosynthetic plan, LFA-1 inhibitors **1** can be derived from iodoimidazoles **2**, which can be accessible from bicyclic guanidine **5**.[4] An intramolecular cyclization of **7** to **5** would be very attractive if more scalable conditions for the cyclization could be defined. In turn, **7** can be readily prepared from **8** by a known procedure.[3] Recently, we disclosed a CuCl-promoted intramolecular cyclization of *N*-(2-aminoaryl)thioureas to 2-(*N*-substituted)amino-benzimidazoles,[7] a class of heterocycles containing the guanidine unit. Therefore, an effort was made to investigate the possibility of CuCl-promoted intramolecular cyclization of thiohydantoins **7** to bicyclic guanidines **5a**–**b** (Scheme 2).

Synthesis of thiohydantoins **7** was outlined in Scheme 3. Highly diastereoselective alkylation was performed by addition of $LiN(TMS)_2$ to a mixture of isobutyraldehyde-derived template **9**[3b] and 4-bromobenzyl bromide or 4-cyanobenzyl bromide at −15 °C to give **10a** and **10b**, respectively. Without purification, deprotection of crude **10a**–**b** was effected by treatment with 50% NaOH and 40% $BnMe_3NOH$ in dioxane at 45 °C, respectively,



Scheme 2.



Scheme 3. Reagents and conditions: (a) $ArCH_2Br$, LHMDS, THF, −15 °C (90–93%); (b) (1) 40% $BnMe_3NOH$, 50% NaOH, dioxane, 45 °C; (2) 6 N HCl, 50 °C (>95%); (c) $BocNHCH_2CO_2H$, *t*-BuCOCl, THF, 0–10 °C (83–85%); (d) $TsOH{\cdot}H_2O$, MeOH, 50 °C (>95%); (e) $CSIm_2$, THF, 20–35 °C (90–93%); (f) CuCl/*i*-Pr_2NEt, Celite, Tol/CH_3CN (10:1), 80 °C (85–92%); (g) $ClP(O)(OEt)_2$, LHMDS, THF, −10 °C (90–95%); (h) TMSCl, NaI, H_2O, CH_2Cl_2, 20 °C (60–65%); (i) *i*-PrMgCl, THF, −20 °C; (2) SO_2, −20 °C; (3) NCS, 5 °C; (4) piperazine, H_2O, 20 °C (85–90%).

followed by addition of 6 N HCl to afford **8a**–**b**. Both **8a** and **8b** were isolated in >80% yield as their *p*-toluenesulfonic acid salts by crystallization from acetonitrile. Both **8a**–**b** then reacted with a mixed anhydride derived from Boc–glycine and pivaloyl chloride in THF to give **11a** and **11b** in 83–85% isolated yield after crystallization from a mixture of heptane and ethyl acetate, respectively. After deprotection of **11a**–**b** with *p*-toluenesulfonic acid monohydride in methanol, addition of the crude amino compounds **12a**–**b** in THF to thiocarbonyl diimidazole afforded thiohydantoins **7a**–**b** in >90% yield. Next, CuCl-promoted cyclization of **7** was studied.

Table 1. Copper(I) salt-promoted cyclization of **7** to **5**

Compound **7**	Reagent	Equivalent	Yield of **5**[a,b,c] (%)
X = Br	CuCl	2.1	85–92
X = Br	CuBr	2.1	65–75
X = Br	$CuBr_2$	2.1	45–57
X = CN	CuCl	2.1	89–93
X = CN	CuI	2.1	60–70
X = CN	$CuCl_2$	2.1	<30

[a] Weight % assay by HPLC.
[b] *i*-Pr_2NEt (2.2 equiv) used.
[c] Reactions run in a mixture of toluene/CH_3CN at 80 °C for 0.5–1 h.

We were pleased to find that copper(I) salts are very effective to promote the cyclization of thiohydantoins **7** to bicyclic guanidine **5** (Table 1). As we already observed in the cyclization of *N*-(2-aminoaryl)thioureas to 2-(*N*-substituted)-aminobenzimidazoles,[7] $CuCl_2$ and $CuBr_2$ were much less effective in promoting this cyclization. Although more air-sensitive copper(I) salts such as CuI and CuBr are fairly efficient in effecting the cyclization, less air-sensitive CuCl and CuBr·SMe_2 provided more consistent results and better yields. The optimized result was obtained with CuCl as promoter.

With the utilization of this CuCl-promoted cyclization to the bicyclic guanidine derivatives, a practical synthesis of LFA-1 inhibitors such as **1a**–**b** was developed (Scheme 3). Thus, the crude thiohydantoins **7a**–**b** from **12a**–**b** were subjected to 2.1 equiv of CuCl in presence of 2.2 equiv of diisopropylethylamine in 10:1 mixture of toluene and acetonitrile at 80 °C for 30 min.[7] A portion of Celite was added to the reaction mixture to facilitate filtration after a complete conversion. Addition of acetonitrile was necessary to facilitate dissolution of both copper(I) chloride and thiohydantoins **7a**–**b** for the cyclization process. After filtration through a pad of active carbon, the crude bicyclic guanidines **5a**–**b** were obtained in >85% yield. Both bicyclic guanidines **5a**–**b** can be isolated by crystallization from toluene in moderate yield.[8] However, it was unnecessary to perform this operation, because the crude products had a purity of >95%. Treatment of crude **5a**–**b** with $LiN(TMS)_2$ in THF at −20 to −10 °C followed by addition of diethyl chlorophosphate gave **6a**–**b** in >90% yield. Without purification, iodination of the crude **6a**–**b** was performed with 4 equiv of TMSCl and 4 equiv of NaI in presence of 2.6 equiv of H_2O in methylene chloride at 20–25 °C for 20 min.[4] Crude iodoimidazoles **2a** and **2b** were purified by crystallization from isopropyl alcohol with a recovery of >40% over five steps from **11**, in both cases. A one-pot operation was developed for conversion of both iodoimidazoles **2a**–**b** to LFA-1 inhibitors **1a**–**b**.[2] Treatment of **2a**–**b** with isopropylmagnesium chloride in THF at −20 °C was followed immediately by addition of SO_2 in THF and NCS, respectively. The resulting mixture was then treated with piperazine in the presence of water to give **1a**–**b** in >85% yield after crystallization.

In summary, the first practical synthesis of a new class of LFA-1 inhibitors has been developed. The key transformations include the CuCl-promoted intramolecular cyclization of thiohydantoins to bicyclic guanidine derivatives, and subsequent iodination of the derived phosphates. This process for iodoimidazoles **2a**–**b** from template **9** involves eight linear steps with only three isolations and an overall yield of 30%. This process has been successfully implemented in the pilot plant to produce multikilogram quantities of LFA-1 inhibitors such as **1a**–**b**.

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8. A typical experimental procedure for CuCl-promoted cyclization of thiohydantoins **7a**–**b** to bicyclic guanidines **5a**–**b**: To a solution of **5a** (175.0 g, 0.35 mol) in a 10:1 mixture of toluene and acetonitrile (800 mL) were added Celite (120 g) and diisopropylethylamine (138.0 mL, 0.80 mol) followed by CuCl (77.2 g, 0.78 mol). The resulting mixture was heated to 80 °C and kept at this temperature for 30 min. After being cooled to 45 °C, the mixture was filtered. The filtrate was treated with active carbon (58 g) at 80 °C for 10 min and filtered through a pad of Celite (30 g). The filtrate was concentrated to a low volume and the residue was dissolved in THF for the next reaction without purification. The weight % assay by HPLC indicated 149.1 g (91%) of **5a** in the solution. An analytical sample of **5a** was obtained by crystallization of the crude from toluene: mp 82–84 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ7.56 (ABq, J = 9.4 Hz, 2H, ArH), 7.34 (s, 1H, ArH), 7.30 (s, 2H, ArH), 6.96 (ABq, J = 9.4 Hz, 2H, ArH), 4.30 (ABq, J = 21.9 Hz, 1H, CH_2CO), 4.19 (ABq, J = 21.9 Hz, 1H, CH_2CO), 3.43 (ABq, J = 13.9 Hz, 1H, $ArCH_2$), 3.25 (ABq, J = 13.9 Hz, 1H, $ArCH_2$), 1.85 (s, 3H, CH_3). ^{13}C NMR (400 MHz, $CDCl_3$): δ 175.0, 174.3, 154.7, 135.6, 132.8, 132.6, 132.1, 131.0, 128.6, 122.7, 122.4, 65.2, 61.4, 40.8, 21.6. MS: *m*/*z* 465 (M^+). Anal. Calcd for $C_{19}H_{14}BrCl_2N_3O_2$: C, 48.85; H, 3.02; Cl, 15.18; N, 9.00. Found: C, 48.75; H, 3.06; Cl, 15.10; N, 8.87. Compound **5b**: mp 79-80 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (ABq, J = 9.5 Hz, 2H, ArH), 7.37 (s, 2H, ArH), 7.25 (ABq, J = 9.5 Hz, 2H, ArH), 7.22 (s, 1H, ArH), 4.33 (ABq, J = 22.0 Hz, 1H, CH_2CO),

4.17 (ABq, $J = 22.0$ Hz, 1H, CH_2CO), 3.54 (ABq, $J = 13.7$ Hz, 1H, $ArCH_2$), 3.37 (ABq, $J = 13.7$ Hz, 1H, $ArCH_2$), 1.87 (s, 3H, CH_3). ^{13}C NMR (400 MHz, $CDCl_3$): δ 174.8, 174.0, 154.4, 139.1, 135.6, 132.8, 132.6, 130.3, 128.6, 122.2, 118.1, 112.3, 64.8, 61.3, 41.3, 21.9. MS: *m*/*z* 413 (M^++1). Anal. Calcd for $C_{20}H_{14}Cl_2N_4O_2$: C, 58.13; H, 3.41; Cl, 17.16; N, 13.56. Found: C, 57.93; H, 3.45; Cl, 17.24; N, 13.56.