Improved Synthesis of a New Nonpeptidic Inhibitor of Human Neutrophil Elastase

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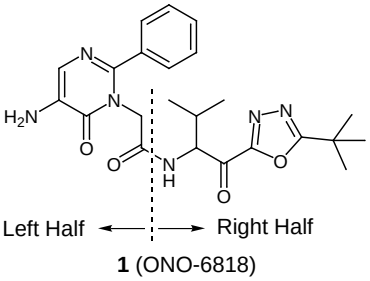
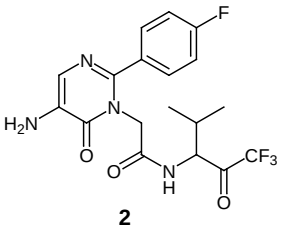
Abstract: A practical method for the synthesis of ONO-6818 {2-(5-Amino-6-oxo-2-phenylhydropyrimidinyl)-*N*-[2-(5-*tert*-butyl-1,3,4-oxadiazol-2-yl)-1-(methylethyl)-2-oxoethyl]acetamide} (**1**), the first clinical candidate for a nonpeptidic orally active inhibitor of human neutrophil elastase (HNE), was developed. This method includes a Lossen rearrangement instead of an explosive Curtius rearrangement and the improved preparation of the α-aminoketone.

Key words: enzyme inhibitor, aminopyrimidinone, ketooxadiazole, Lossen rearrangement, anionic addition reaction



1 (ONO-6818)



2

Figure 5-Amino-2-phenylpyrimidin-6-ones: Orally Active Inhibitors of HNE

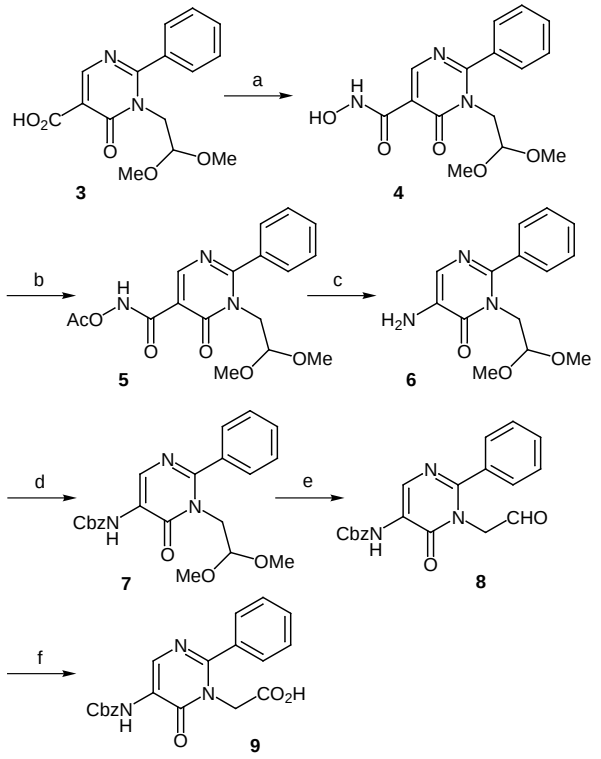
Human neutrophil elastase (HNE) is a serine protease released by human neutrophils in response to inflammatory stimuli.[1] It has been implicated in the development of various diseases such as emphysema,[2] adult respiratory distress syndrome (ARDS), cystic fibrosis,[3] and rheumatoid arthritis. In excess, HNE hydrolyses elastin, the structural protein which gives the lungs their elasticity, and may cause tissue damage and the development of the diseases mentioned above. It has been postulated that a small molecular weight inhibitor of HNE could restore this imbalance, and would be beneficial for the treatment of such diseases. A variety of structural classes of inhibitors of HNE have thus been studied.[4] But orally active ones possessing clinical potential are very rare. In fact, peptidyl trifluoromethyl ketone inhibitor reported by Zeneca[5] was the only example until recently. 2-Phenyl-pyrimidinone-α-keto-1,3,4-oxadiazole **1** (ONO-6818) is a nonpeptidic orally active inhibitor of HNE that is currently being evaluated in clinical trials (phase I).[6] Pharmacological data (Table) indicate **1** to be a clinically useful drug on the basis of its excellent oral profiles relative to **2**.[7] Cost-effective production of **1** has been our urgent requirement because of the remarkable increase in demand for further clinical evaluation. Removal of the explosive Curtius rearrangement, which was included in the previously reported method,[8] was needed for the development of a cost-effective method of synthesizing **1**. The tedious reaction process (**10** → **18a** → **18b** → **19a** → **19b** → **19c** → **15**: 6 steps in all) for the synthesis of **15** also had to be improved.[6]

In this paper, we describe a practical method for the synthesis of **1**, the first clinical candidate for an orally active nonpeptidic inhibitor of HNE. The overall reaction schemes are outlined in Schemes 1 and 2. Compound **3**, prepared according to the reported method,[8] was converted to the corresponding hydroxamic acid **4**. Lossen rearrangement of **5**, prepared by *O*-acetylation of **4** followed by the aqueous hydrolysis of the formed isocyanate, afforded an amine **6**. Protection of the newly formed amine group of **6** by a benzyloxy carbonyl group afforded **7**. Acidic deprotection of the dimethyl acetal of **7** produced an aldehyde **8**. Oxidation of the aldehyde **8** to a carboxylic acid **9** was accomplished upon the treatment of **8** with sodium chlorite in water.

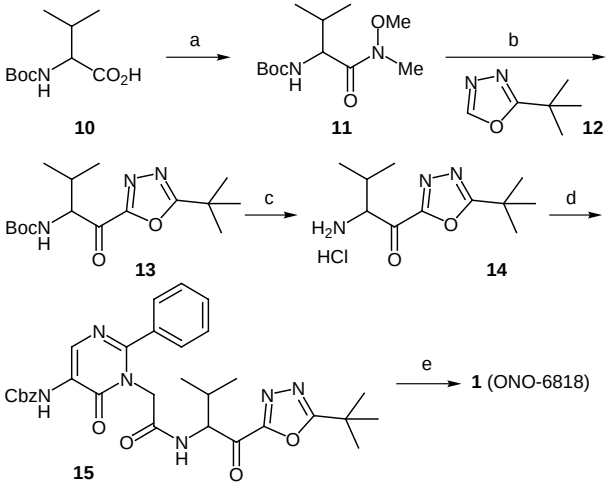
Table Biological data of **1** (ONO-6818) and **2**

Compd.	*K*i (nM)[a]	ED_{50} (mg/kg, po)[b]
1	12	1.4
2	101[c]	7.5[c]

[a] Inhibition of HNE-catalyzed hydrolysis of the synthetic substrate MeO-Suc-Ala-Ala-Pro-Val-pNa. [b] Inhibition of HNE-induced lung hemorrhage in hamsters. Test compounds were administered orally 1h before intratracheal instillation of HNE (10 U / lung). [c] See ref 7.

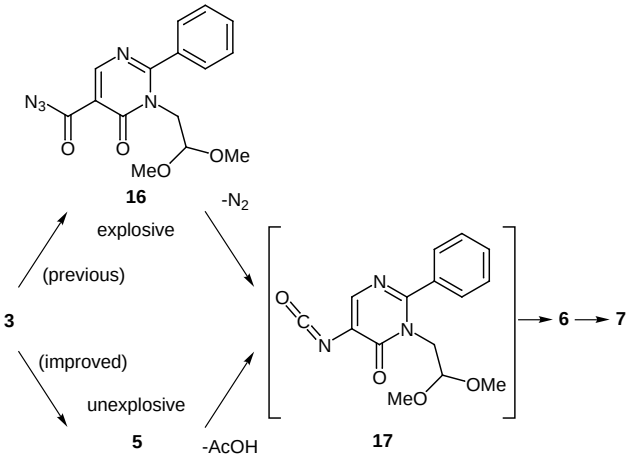


Scheme 1 Unexplosive Method to Prepare the Left Half **9**
Reagents: (a) 1) isobutyl chloroformate, triethylamine, THF, 0 °C, 1 h, 2) 50% hydroxylamine-H_2O, 0 °C, 20 min, 91%; (b) acetic anhydride, pyridine, THF, rt, 20 min; (c) 1,8-diazabicyclo[5.4.0]-7-undecene, THF, H_2O, reflux, 1 h; (d) benzyloxycarbonyl chloride, $NaHCO_3$, THF, H_2O, 0 °C, overnight; (e) 1N HCl, acetic acid, 70 °C, 2 h; (f) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O, 0 °C → rt, 3 h, 63% in 5 steps.

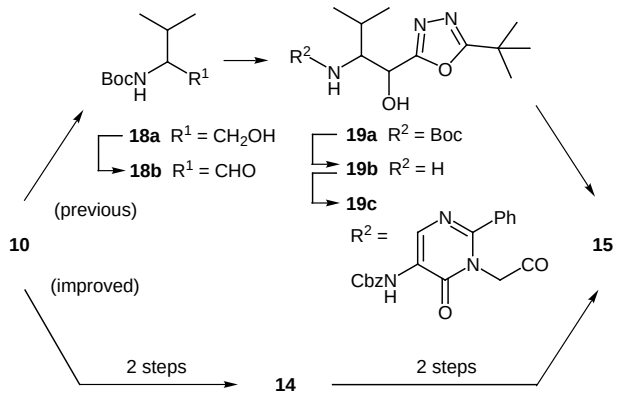


Scheme 2 Synthesis of **1** (ONO-6818) Including the Improved Synthesis of the Right Half **14**
Reagents: (a) *N,O*-dimethylhydroxylamine hydrochloride, EDC•HCl, pyridine, 0 °C → rt, 2 h, 86%; (b) **12**, LDA, TMEDA, THF, -70 °C → -20 °C, 5 h; (c) 4N HCl-EtOAc, 10 ~ 20 °C, 3 h, 86% in 2 steps; (d) **9**, ethyl chloroformate, *N*-methylmorpholine, THF, -5 °C, 1 h, 98%; (e) H_2 (3 atm), 10% Pd/C (50% wet), MeOH, rt, 25 min, 77%.

Scheme 3 Summary of the Improvement



a) Replacement of the Explosive Curtius Rearrangement with an Unexplosive Lossen Rearrangement: Improved Synthesis of **7**



b) Improvement in the Synthesis of the Intermediate **15**

Improved synthesis of the right half **14** starting from Boc-valine (**10**) was accomplished as described in Scheme 2. Direct coupling reaction of the Weinreb amide **11**, prepared from **10**, with anion of **12** afforded **13**, which was converted to the right half **14** by acidic deprotection. Condensation of **9** with **14** was carried out by a mixed anhydride method to give **15**. Deprotective hydrogenation of **15** provided **1** (ONO-6818) in good yield.

The above-described synthetic improvement is summarized in Scheme 3. Scale-up synthesis of **7** was problematic because of the explosiveness of the Curtius rearrangement evolving nitrogen gas. The Lossen rearrangement which forms acetic acid instead of nitrogen gas is a feasible candidate as a substitute for the Curtius rearrangement.[9]

As shown in Scheme 3a, the explosive Curtius rearrangement was replaced by an unexplosive Lossen rearrangement in the synthesis of **7** whose deprotection afforded **8**. The previous method of synthesizing **7** via **16** included an explosive rearrangement reaction of **16** to form the isocy-

anate **17** followed by the addition reaction of benzyl alcohol to the formed isocyanate **17**.[8]

Synthesis of **15** from **10** was also improved as described in Scheme 3b. The previous method consisting of 6 steps via **18** and **19** was replaced by a new 4 step-synthesis via aminoketone **14** as described in Scheme 2.

All the steps were carried out without column chromatography on silica gel. Thus, practical synthesis of ONO-6818 (**1**), the first clinical candidate for an orally active non-peptidic inhibitor of HNE, was successfully carried out. This method involves the unexplosive Lossen rearrangement of **5** instead of an explosive Curtius rearrangement and the direct coupling reaction of Weinreb amide **11** and the anion of **12** to form the right half **14**.

Full details regarding the right half will be reported in due course.[9]

References and Notes

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(9) Full details regarding the right half will be reported in *J. Heterocycl. Chem.*

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