Bioorganic & Medicinal Chemistry Letters, Vol.3, No.2, pp. 305-308, 1993
Printed in Great Britain

0960-894X/93 $6.00 + .00

SYNTHESIS OF NEW AMIDE-LINKED *N*-HYDROXYUREA 5-LIPOXYGENASE INHIBITORS BY AN INTRAMOLECULAR OXYGEN TO NITROGEN ACYL TRANSFER

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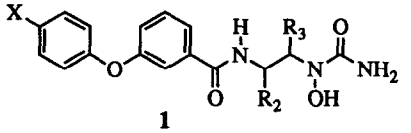
(*Received in USA 5 November* 1992)

Abstract: A convergent and efficient synthesis of amide-linked *N*-hydroxyurea 5-lipoxygenase inhibitors is reported. The synthesis involves a one-pot, three-step procedure where an appropriately substituted *N*-hydroxy-*N*-[2-((*tert*-butyloxycarbonyl)amino)ethyl]urea is *O*-acylated with the desired acid chloride. The *O*-acyl intermediate was *N*-deprotected *in situ*, and the resulting amine salt neutralized to induce an intramolecular acyl transfer from oxygen to nitrogen.

Recently we were faced with the task of preparing and screening the 5-lipoxygenase inhibitory activity of a diverse array of amide-linked *N*-hydroxyureas **1**.[1] These compounds were designed as bioisosteres of the corresponding olefin-linked *N*-hydroxyureas (e.g. **2**) which have been described in the literature as potent and orally active inhibitors of 5-lipoxygenase.[2] Compound **3** was selected as the intial target for developing a synthesis for



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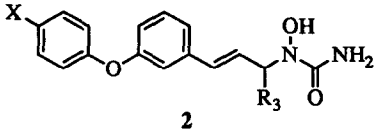
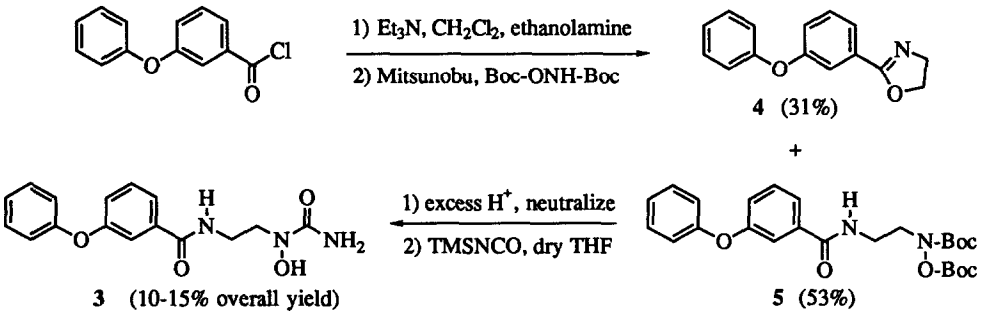


2

this new class of compounds. A linear approach was undertaken where ethanolamine was *N*-acylated with 3-phenoxybenzoyl chloride. A Mitsunobu reaction with *N,O*-bis-*tert*-(butyloxycarbonyl)hydroxylamine was employed to introduce a protected form of hydroxylamine. Subsequent deprotection, neutralization, and treatment with *N*-trimethylsilylisocyanate delivered the desired prototype **3** in a 10-15% overall yield from the starting acid chloride (Scheme I). Further investigation revealed that the low yield was due, in part, to the competitive

Scheme I

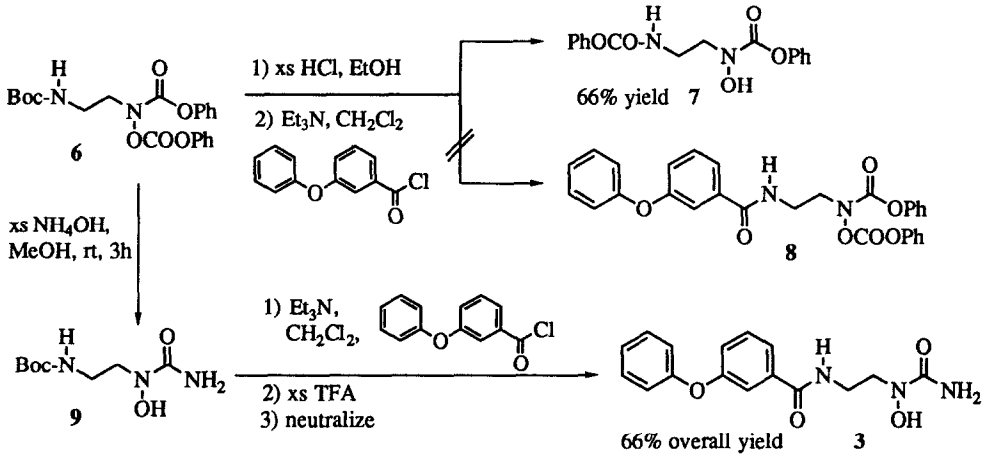


cyclodehydration in the Mitsunobu reaction to give a mixture of the oxazoline,[3] **4** (31%), and the desired product **5** (53%).[4] Oxazoline yields, in other examples, varied between 15-50%. In all examples studied, the combined yield of the Mitsunobu product and oxazoline were 80-90%. Experimental conditions to predictably minimize this

competitive process could not be identified. Furthermore, the sequence was not amenable to scale-up. A new synthetic sequence was therefore sought.

A second approach was undertaken where the amino-group and the hydroxylamine were orthogonally protected, expecting that selective deprotection of the amino-group and subsequent acylation with the desired acid chloride could be achieved. Mitsunobu reaction of *N*-Boc-ethanolamine with *N,O*-bis(phenoxycarbonyl) hydroxylamine[5] efficiently provided the desired orthogonally diprotected urea precursor **6** (90% from ethanolamine). The Boc-group could be cleanly deprotected by exposure to HCl in ethanol (10 equiv., ambient temperature, 1-2 h) and the resulting amine salt isolated by simply removing the volatiles under vacuum. A mixture was obtained when *N*-acylation was attempted by *in situ* neutralization of the amine hydrochloride salt, with triethylamine, in the presence of 3-phenoxybenzoyl chloride. The major product was **7** (66%), rather than the desired product, **8** (Scheme II). This unexpected result suggested that if **9** could be selectively *O*-acylated with the desired acid chloride, subsequent *N*-deprotection and neutralization potentially could provide the desired inhibitor **3**, after an oxygen to nitrogen acyl transfer.[6]

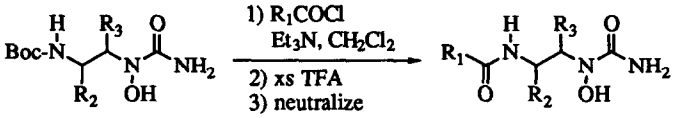
Scheme II



Preparation of *N*-hydroxy-*N*-[2-((*tert*-butyloxycarbonyl)amino)ethyl]urea (**9**) was easily accomplished by exposure of **6** to ammonium hydroxide in methanol (50-66%). Exposure of **9** to 3-phenoxybenzoyl chloride (1.1 equiv.) in the presence of triethylamine (1.5 equiv.), a catalytic amount of 4-dimethylaminopyridine, in dichloromethane (0.25 M), at ambient temperature led to selective *O*-acylation after one hour. To the reaction solution was added trifluoroacetic acid (equal in volume to the dichloromethane) and the resulting solution was stirred for 0.5 h. The volatiles were removed under vacuum. The resulting residue was dissolved in benzene (20 mL) and concentrated under vacuum (2 cycles) to remove the triflouroacetic acid, then dissolved in dichloromethane (0.25 M). Triethylamine (3 equiv.) and excess aqueous saturated sodium bicarbonate were added. The desired compound was isolated by a normal extractive process after stirring for one hour at ambient temperature to provide a 66% yield of **3** after recrystallization. The Table summarizes the results for representative acid chlorides in this convergent, one-pot, three-step procedure for the preparation of amide-linked *N*-hydroxyureas.

The method is fairly general in that aryl-, alkyl-, and α,β–unsaturated acid chlorides are amenable to this procedure. Aryl acid chlorides tend to give higher yields. Branching substituents on the starting *N*-hydroxyurea (i.e. R_2 and R_3) seem to have little or no effect on the yield. The lower yielding examples tend to give incomplete oxygen acylation.[7]

PREPARATION OF AMIDE-LINKED *N*-HYDROXYUREAS
VIA AN OXYGEN TO NITROGEN ACYL TRANSFER



Entry	R_1	R_2	R_3	*N*-Hydroxyurea Yield %[a]
1	3-phenoxybenzoyl	H	H	66
2	3-(4-fluorophenoxy)benzoyl	H	H	60
3	3-(4-fluorophenoxy)benzoyl	Me	H	70
4	3-(4-fluorophenoxy)benzoyl	H	Me	61
5	benzoyl	H	H	40
6	4-methoxybenzoyl	H	H	45
7	4-cyanobenzoyl	H	H	45
8	2-methylbenzoyl	H	H	76
9	2,6-dimethylbenzoyl	H	H	0[b]
10	3,3-dimethylacryloyl	H	H	27
11	*n*-hexanoyl	H	H	22
12	pivaloyl	H	H	29

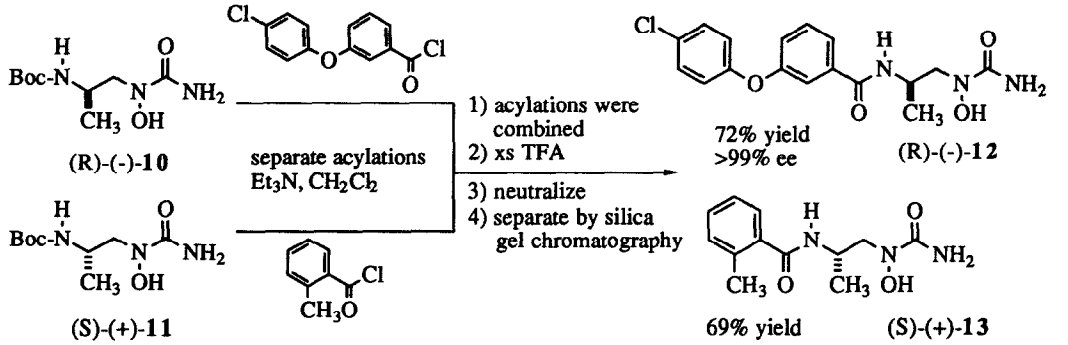
a) Yields refer to homogeneous products obtained after chromatography over silica gel and have been characterized by PMR, mass spectral analysis, and elemental analysis. b) No acylation was observed.

The oxygen to nitrogen acyl transfer was assumed to occur intramolecularly since this would involve a six-membered transition structure. To validate this hypothesis, (R)-(-)- and (S)-(+)-alaninol were converted, as previously described, to their respective optically active *N*-Boc-hydroxyurea derivatives (R)-(-)-**10** and (S)-(+)-**11**. Acylation of (R)-(-)-**10** with 3-(4-chlorophenoxy)benzoyl chloride and of (S)-(+)-**11** with 2-methylbenzoyl chloride were carried out independently at 0.25M in dichloromethane. Equal volumes of the two solutions were transferred to a new flask where the oxygen-acylated intermediates were then deprotected and neutralized as previously described. The two final products were separated by flash chromatography to give (-)-**12** (72%) and (+)-**13** (69%) (Scheme III). Chiral HPLC analysis of (-)-**12** obtained from the mixture of **12** and **13**, and authentic samples of (+)- and (-)-**12** revealed no detectable trace of the crossover isomer, (+)-**12**, thus indicating that the oxygen to nitrogen acyl transfer is indeed an intramolecular process.

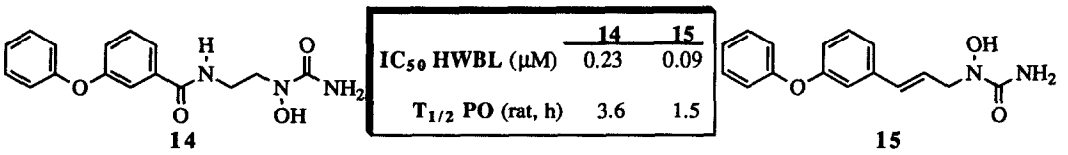
We have successfully developed a rapid, efficient, and convergent synthesis of amide-linked *N*-hydroxyureas (**1**) which involves an intramolecular oxygen to nitrogen transfer of an *O*-acyl *N*-hydroxyurea precursor. To the

best of our knowledge this represents the first intramolecular use of an *O*-acyl hydroxamate derivative as an acylating agent. The process has been shown to be generally applicable to a wide variety of acid chlorides. The

Scheme III



product from entry 1, **14**, compares quite favorably with the corresponding olefin *N*-hydroxyurea, **15**, with regard to inhibition of leukotriene biosynthesis in human whole blood and half-life after dosing orally in rats. Further SAR and bioactivity details will be forthcoming.



	14	15
IC_{50} HWBL (μM)	0.23	0.09
$T_{1/2}$ PO (rat, h)	3.6	1.5

Acknowledgments. The expert assistance of Michael Fitzgerald in obtaining the chiral HPLC results is gratefully acknowledged. The spectroscopic and analytical support from Department 417 is also acknowledged.

Footnotes and References

1) A preliminary account of SAR for this series was recently presented: Dellaria, J. F.; Sallin, K. J.; Moore, J. L.; Bell, R. L.; Lanni, C.; Bouska, J.; Young, P. R.; Brooks, D. W.; Carter, G. W. *Abstracts of Papers*, 204th American Chemical Society National Meeting, Washington, DC; American Chemical Society: Washington, DC, 1992; abstract Medi 104.

(2) Garland, L. G.; Jackson, W. P.; Salmon, J. A.; Nicholls, A. *Abstracts of Papers*, 199th American Chemical Society National Meeting, Boston, Massachusetts; American Chemical Society: Boston, MA, 1990; abstract Medi 149.

(3) Preparation of oxazolines via the Mitsunobu cyclodehydration of hydroxyamides has recently been reported; please see: Galeotti, N.; Montagne, C.; Poncet, J.; Jouin, P. *Tetrahedron Lett.* **1992**, *33*, 2807-2810.

(4) The oxazoline and Mitsunobu product were partially separable by silica gel chromatography. The ratio of the two products was established by PMR on the unpurified reaction mixture. The yields were calculated based on the mixture obtained after chromatography. The mixture can be converted to the corresponding *N*-hydroxyurea where the oxazoline may be removed.

(5) Stewart, A. O.; Brooks, D. W. *J. Org. Chem.* **1992**, *57*, 5020-5023.

(6) a) *N*-hydroxysuccinimide esters have been used as active esters for the acylation of amines in peptide synthesis. For a brief overview please see: Klausner, Y. S.; Bodansky, M. *Synthesis* **1972**, 453-463. b) To the best of our knowledge this represents the first intramolecular application of an hydroxamate active ester as an acylating agent.

(7) It is interesting to note that adding excess acid chloride did not improve the yield. As a representative case, it was estimated that when 1.1 equivalents of benzoyl chloride were employed the Boc-*N*-hydroxyurea was ~70-80% acylated. Additional benzoyl chloride was added until the Boc-*N*-hydroxyurea was consumed.