Pergamon

Tetrahedron Letters, Vol. 38, No. 28, pp. 4981-4984, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01080-0

Substituted 2,3-Dihydroisoxazoles (Δ^4-Isoxazolines) *via* Palladium-mediated Cyclization of Propargylic N-Hydroxyureas.

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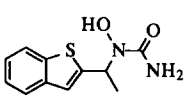
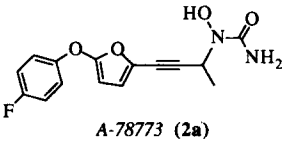
Abstract: Aryl-substituted propargylic N-hydroxyureas cyclize in the presence of catalytic $Pd(OAc)_2$ to yield 2,3-dihydroisoxazoles. © 1997 Elsevier Science Ltd.

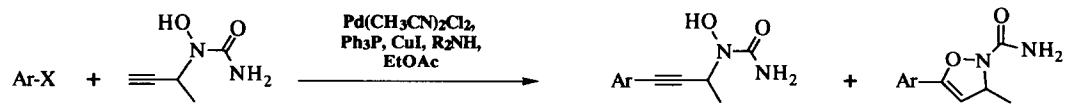
Abbott Laboratories, along with many other research groups, has been actively investigating substituted hydroxylamine derivatives as inhibitors of the enzyme 5-lipoxygenase (5-LO). These compounds represent a promising new clinical treatment for a variety of leukotriene-mediated disorders such as asthma, inflammatory bowel disease, and rheumatoid arthritis. The arylalkyl N-hydroxyurea substructure of Abbott's first generation 5-LO inhibitor, Zileuton (**1**),[1] is common to a number of other inhibitor candidates.[2] Research subsequently shifted to compounds which incorporate an acetylenic or vinylic "spacer" between the aryl ring and the alkylhydroxylamine derivative.[3] Compound **2a**, A-78773 (previously under development at Abbott), is typical of these compounds. Rapid access to compounds of type **2** is readily accomplished by using a variant of the Castro-Stephens coupling[4,5] of an aryl halide (**3**) and propargylic N-hydroxyurea **4**.[2e,6]



Zileuton (**1**)

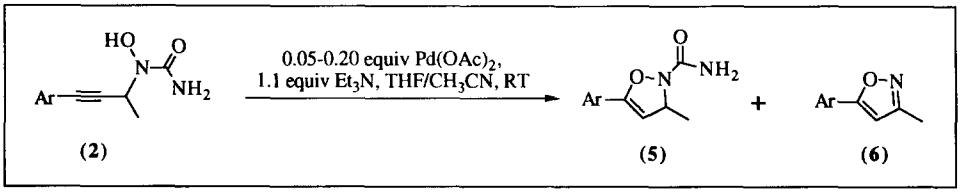


A-78773 (**2a**)



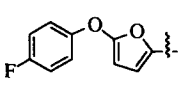
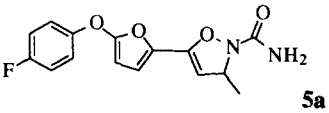
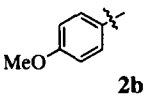
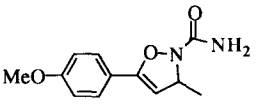
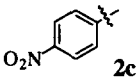
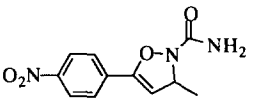
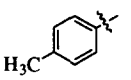
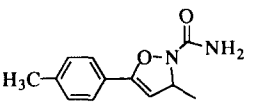
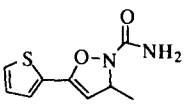
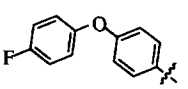
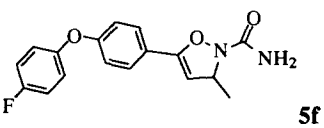
(**3**) (**4**) (**2**) (**5**)

During the process development of these second generation 5-LO inhibitors, 2,3-dihydroisoxazoles (**5**) were detected as significant by-products in the palladium coupling reactions. Initially, it was found that the formation of these compounds could be limited by attenuating the activity of the catalyst, $Pd(CH_3CN)_2Cl_2$,



(2) (5) (6)

Table 1: Cyclization of Propargylic N-Hydroxyureas

Starting Material (Ar =)	Product	Yield[a]
 **2a**	 **5a**	**87**
 **2b**	 **5b**	**80**
 **2c**	 **5c**	**56 (99)[b]**
 **2d**	 **5d**	**53**
 **2e**	 **5e**	**50**
 **2f**	 **5f**	**65**

Notes: [a] All compounds were isolated by silica gel chromatography and characterized by ^{1}H and ^{13}C NMR, IR, and MS. [b] Higher yield based on recovered starting material.

with Ph_3P. We felt however that the formation of these 2,3-dihydroisoxazoles represented an opportunity to explore the chemistry of the N-hydroxyurea moiety, a substituent common to many potential 5-LO inhibitors. We therefore set out to determine the optimal conditions for their formation. As anticipated, we found it was possible to increase the yield of dihydroisoxazoles to a certain extent by the use of a stronger catalyst, like $Pd(OAc)_2$, or more robust reaction conditions, such as higher temperatures and larger catalyst loadings.

Unfortunately, these efforts also generated considerably more degradation products. Not surprisingly therefore, we obtained the best yields when the intermediate N-hydroxyurea (**2**) was first isolated and then separately exposed to the cyclization conditions. As illustrated in Table 1, a variety of aryl-substituted propargylic N-hydroxyureas (**2**) undergo facile cyclization to the corresponding 2,3-dihydroisoxazoles (**5**). The products of other cyclization pathways (leading to the formation of 6-membered heterocycles) were not observed. Although racemic N-hydroxyurea **4** was used for this study, we expect cyclizations with enantiomerically pure material to proceed with retention of configuration.

We were surprised to find that this retrosynthetic disconnection of the 2,3-dihydroisoxazole ring system is not one commonly employed.[7] The majority of synthetic approaches to dihydroisoxazoles tend to fall into two groups: the [2+3] dipolar cycloaddition of nitrones and alkynes[8] constitutes the majority of these synthetic methods, while the functionalization or reduction of isoxazolium salts[9] accounts for most of the remainder. A small number of other methods have been reported, with very few instances of a functionalized hydroxylamine cyclizing onto an adjacent alkyne.[10] In these few methods, strong base is typically employed to facilitate the ring closure. Although there are examples of this type of electrophilically-induced cyclization with respect to other heteroatoms,[11] we were unable to find an example utilizing a hydroxylamine.

The cyclizations described proceeded using 0.05 to 0.20 equiv of $Pd(OAc)_2$ in the presence of a slight molar excess of Et_3N in THF. Acetonitrile was added to the reaction mixture to improve the solubility of certain N-hydroxyureas. These cyclizations proceeded slowly, typically requiring from 12-48 hrs to go to completion. The rate of reaction can be increased by using larger amounts of catalyst or with gentle heating (30 - 35 °C), however these can result in more reaction by-products. Under the conditions described, the reactions were reasonably clean; the major by-products being small amounts of the corresponding isoxazoles (**6**), unreacted starting material (in certain instances) and a number of trace unidentified compounds. Despite their presence in small quantites (1-10% depending upon the case), the formation of aryl-substituted isoxazoles (**6**) was intriguing. Although we were unable to find a simple method to prevent their formation, we did find that higher reaction temperatures, and larger excesses of base tended to increase the amount of **6** formed.

We expected a certain degree of decomposition in each case, as we had found earlier that the parent compound, N-hydroxyurea **4**, underwent extensive degradation to unidentified products when exposed to $Pd(OAc)_2$. It is therefore likely that only sufficiently activated N-hydroxyureas of type **2** will cleanly participate in this chemistry. It is noteworthy that aromatic rings substituted with either electron-donating or electron-withdrawing groups undergo cyclization. We did observe, however, that nitro-derivative **2c** cyclized at a considerably slower rate than the other examples. The biological activity of the dihydroisoxazoles formed in these cyclizations is unknown. A typical experimental is described below.[12]

Thienyl Dihydroisoxazole 5e. N-Hydroxyurea **2e**[13] (1.96 g, 9.33 mmol), $Pd(OAc)_2$ (0.10 g, 0.49 mmol, 0.052 equiv), Et_3N (1.4 mL, 10 mmol, 1.1 equiv), 10 mL of THF and 10 mL of CH_3CN were placed in a 50-mL, one-necked, round-bottomed flask. The reaction mixture was stirred under a nitrogen atmosphere at rt. When the reaction was deemed complete by TLC (about 24 hours), the entire reaction mixture was filtered through a 1 inch plug of silica gel, which was rinsed 3 times with 25 mL of ethyl acetate. This filtrate was

evaporated to afford 1.68 g of a dark colored oil. The oil was purified by chromatography on silica gel (elution with 50% ethyl acetate in heptanes) affording 0.98 g (50%) of a colorless solid, mp 95 - 96 °C (uncorrected).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.34 (dd, ^{4}J=1.1Hz, ^{3}J=5.1Hz, 1H), 7.24 (dd, ^{4}J=1.1Hz, ^{3}J=3.7Hz, 1H), 7.05 (dd, ^{3}J=3.7Hz, ^{3}J=5.1Hz, 1H), 5.60 (br s, 2H), 5.32 (d, ^{3}J=2.7Hz, 1H), 5.24 (dq, ^{3}J=2.7Hz, ^{3}J=6.3Hz, 1H), 1.40 (d, ^{3}J=6.3Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.8, 147.0, 129.1, 127.3, 126.3, 125.6, 99.0, 61.5, 22.2. MS (CI, NH_3) 421 (2M + H^+) , 228 (M + NH_4^+), 211 (M + H^+). Anal Calc'd for $C_9H_{10}N_2O_2S$: C, 51.41; H, 4.79; N 13.32; S, 15.24. Found: C, 51.47; H, 4.77; N 13.03; S, 15.01.

Acknowledgments:
We wish to acknowledge the contributions of our colleagues in the Process-Analytical Support and Process Research and Development departments. We are grateful to Elaine Wiggins for assistance with elemental analyses. We also wish to thank Dr. David P. Sawick and Dr. David R. Hill for their valuable suggestions.

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11 Tsuji, J. *Organic Synthesis with Palladium Compounds;* Springer-Verlag: New York, 1980.
12 Larger scale experiments are typically quenched with 10% aqueous NH_4OH to facilitate the removal of palladium and copper salts. The crude product is then isolated by extraction with ethyl acetate or a similar solvent. In all cases, the crude products were purified by column chromatography.
13 Prepared from 2-iodothiophene and **4** as described in references 2e and 5.

(*Received in USA* 20 *April* 1997; *accepted* 28 *May* 1997)