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SYNTHESIS OF SUBSTITUTED HETEROCYCLES. SIMPLE METHOD FOR THE INTRODUCTION OF THE N-HYDROXYUREA FUNCTIONALITY

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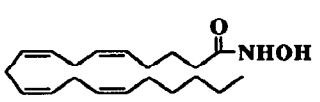
Abstract: A simple method for the introduction of the N-hydroxyurea functionality has been developed. This involves conjugate addition of hydroxylamine to a vinylsulfone substrate. This method was successfully used in a facile synthesis of the 5-lipoxygenase inhibitors, zileuton and A-69412.

A variety of 5-lipoxygenase inhibitors have been the research focus of several groups. Examples of these compounds are arachidonate hydroxamic acid **1**,[1] MK-886 **2**,[2] zileuton **3** [3] and A-69412 **4**. Zileuton and A-69412 contain an N-hydroxyurea as a necessary component for biological activity. [3] Our research efforts have been directed toward an efficient synthesis of **3** and **4**.



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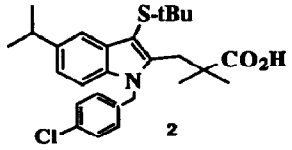

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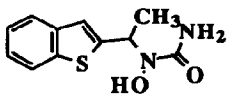

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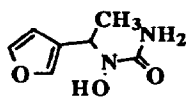

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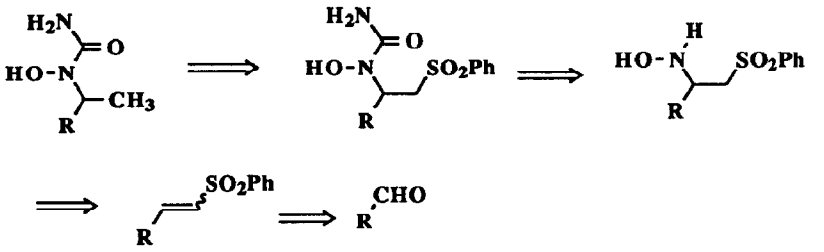
The most common method for preparation of an N-hydroxyurea is by treatment of an N-hydroxylamine with potassium isocyanate in the presence of acid. The hydroxylamine can be prepared by one of several methods: (1) acid catalyzed reduction of an oxime; [4] (2) addition of an organolithium compound to an oxime [5]

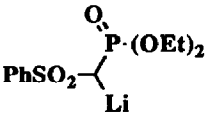
in the presence of BF_3OEt_2; [6] or (3) displacement of a leaving group with hydroxylamine. All of these methods suffer from a variety of drawbacks. Method (1) is highly dependant on the nature of the reducing agent whereas methods (2) and (3) yield product in low yields.

For the synthesis of **4**, method (1), utilizing pyridine borane, proved the easiest route, initially. Unfortunately, over 5 equivalents were needed to drive the reaction to completion. Other reducing methods were investigated but none yielded satisfactory results. It was also noted that the hydroxylamine was highly soluble in water which made isolation tedious and usually led to lower yields. Neither method (2) nor (3) were practical in our hands. These problems forced the development of a new synthetic approach for the hydroxylamine. The basis for our new protocol centered on the use of an appropriately substituted vinyl sulfone which could accept a functional group pre-disposed for conversion to an N-hydroxyurea (Scheme 1).

Scheme 1



Scheme 2 details the synthesis. The vinyl sulfones were easily prepared via a Wittig-Horner olefin synthesis by reaction of the appropriate aldehyde (**5a** or **b**) with reagent **6** [7] to give the vinyl sulfone derivatives **7**.[8] Once the vinyl sulfones were in hand, the hydroxylamines were prepared by conjugate addition of either hydroxylamine or an O-protected hydroxylamine. For example, **7a** was reacted with hydroxylamine



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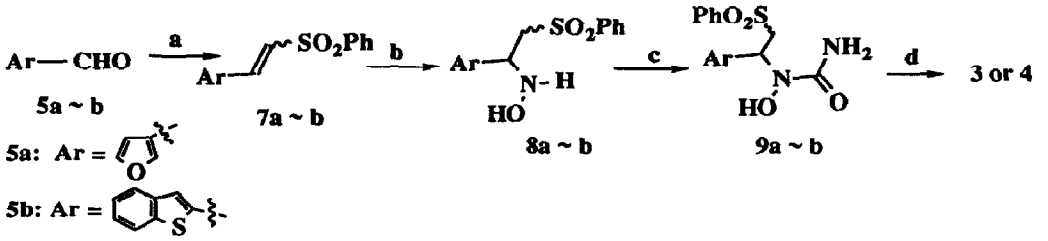
hydrochloride in the presence of K_2CO_3 in THF to give **8a**. Without further purification, this hydroxylamine was reacted with potassium isocyanate to give **9a**. **7b** was reacted with O-trimethylsilyl hydroxylamine to give **8b** which was converted to **9b** after reaction with trimethylsilyl isocyanate.

Removal of the sulfonyl group in the case of **9a** was easily achieved by simple treatment with magnesium in methanol to give **3**. In the case of **9b**, desulfonylation was not straight forward. Selective removal of the sulfone without decomposition was difficult, presumably through destruction of the benzothiophene core. A variety of desulfonylation methods were investigated (Mg^0/MeOH; [9] Na/Hg, MeOH, NaH_2PO_4;[10] NaHTe, DMF or NaHTe, EtOH;[11] SmI_2, THF;[12] $Na_2S_2O_4$, $NaHCO_3$, DMF;[13] Zn, HOAc;[14] Al/Hg, MeOH, NaH_2PO_4;[15] Ra-Ni, EtOH;[16] Bu_3SnH, AIBN, Toluene[17]). Of these methods, it was found that desulfonylation occurred most readily with buffered Na/Hg (Na_2HPO_4, THF, H_2O) [10] to give **3**.

Scheme 2



Reagent: a) 6, LDA, THF, -78°C for 5a to 7a(80%), for 5b to 7b (83%); b) NH_2OH. HCl, K_2CO_3, THF, 40°C for 7a to 8a (82%), $TMSONH_2$, THF, r.t. for 7b to 8b (85%); c) KCNO, EtOAc, HCl, r.t. for 8b to 9b (79%) or TMSNCO, THF, r.t. for 8b to 9b (85%); d) Mg/MeOH, reflux for 3h for 9a to 4 (87%), 2.2% Na/Hg, Na2HPO4, MeOH for 9b to 3 (81%)

We have presented here a simple method for the introduction of the N-hydroxylamine moiety to a heterocyclic system. The vinylsulfone substrate is readily available from the corresponding aldehyde and can be easily converted to its N-hydroxylamine derivative. Once converted to the N-hydroxyurea, desulfonylation liberates the desired product. This method is currently being investigated as a general method for the introduction of the N-hydroxyurea functionality to other interesting substrates.

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7. Reagent **6** prepared as follows:

$$PhSO_2CH_3 \xrightarrow[2)\ (EtO)_2POCl]{1)\ LDA,\ THF,\ -78^{\circ}C} \mathbf{6}\ \text{(not isolated)}$$

This is an extrapolation of the Wittig-Horner modification of the Wittig olefin synthesis described in: Camins, D.L.; Jacobine, A.F.; Marshall, J.L.; Turnbull, M.M. *Synthesis* **1978**, 309. For more information on the preparation and application of vinyl sulfones, see: Simpkind, N.S. *Tetrahedron*, **1990**, *46*, 6951.

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