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Synthesis of N-allylhydroxamic Acids via [3,3]-Sigmatropic Rearrangement[1]

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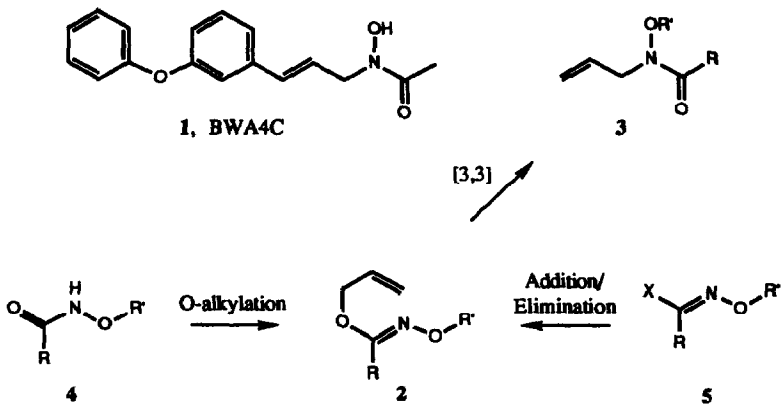
Abstract: N-allylhydroxamic acids **3** can be prepared by a novel thermal [3,3]-rearrangement of appropriate precursor O-tetrahydropyranylhydroximates **2**. Such compounds are available from the protected hydroximoyl chlorides via alkoxide displacement. The rearrangement can proceed with modest chirality transfer.

Interest in the N-allylhydroxamic acid functionality derives from recent findings that show good 5-lipoxygenase inhibitory activity for compounds such as Burroughs Welcome's BWA4C **1**.[2] Consideration of synthetic approaches to these targets leads naturally to a route via [3,3] sigmatropic rearrangement (**2** → **3**)(Scheme 1). For such "aza-rearrangements", Overman's trichloroimidate[3a] methodology provides a seminal example and other cases have been reported.[3] Nevertheless, we are not aware of any previous examples of this particular utilization of the aza-Claisen rearrangement.

Scheme 1



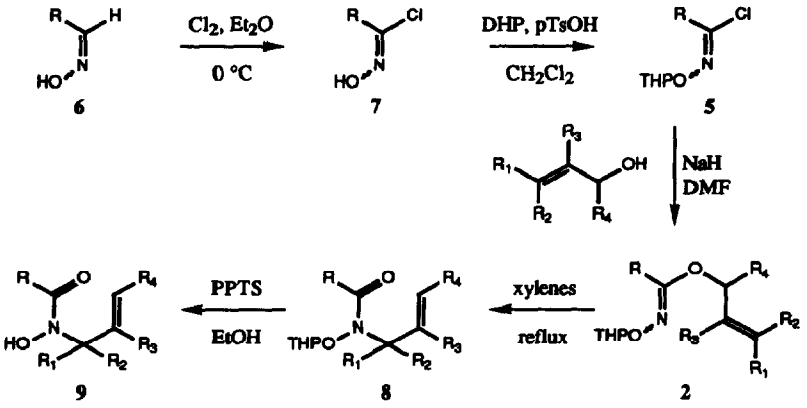
1, BWA4C **3** **4** **2** **5**

Initially, we obtained proof of feasibility for this rearrangement using the known allyl O-propylbenzohydroximate **2** (R = Ph, R' = Pr). This substrate was prepared by direct allylation of the silver salt of propyl benzohydroxamate with allyl bromide as reported in the literature (**4** → **2**).[4] Subsequent

rearrangement occurred smoothly albeit slowly (24 hr) in refluxing xylene to furnish the desired N-allylhydroxamate **3** (R = Ph, R' = Pr) in > 80% yield.

The general utility of the O-alkylation protocol to prepare compounds **2** is limited by several factors. First, the need to prepare highly functionalized halides or sulfonates with high regio- and stereocontrol could become problematic. Second, preparation of the silver salt in a separate step reduces the attractiveness of the route. Finally, the desired product is always accompanied by undesired N-alkylation product, which can lead to overall loss of regioselectivity for the process. For these reasons, we chose to pursue the displacement route (**5** → **2**). Recent literature precedent[5] for this type of displacement in a simple system is available (R' = CH_2Ph, R = Me, X = Cl) and guided development of our strategy (Scheme 2).

Scheme 2



Successful application of this scheme was realized using THP protection of the hydroxamate. This protecting group was chosen over benzyl and other possible protecting groups for relative ease of addition and removal, especially in consideration of the olefinic functionality present in the final products. Thus, chlorination[6] of benzaldehyde oxime **6** was carried out in Et_2O by slow introduction of a CCl_4 solution of Cl_2 at 0° C. Due to the relative instability[7] of benzohydroximoyl chloride **7**, chlorination was followed by minimal workup (removal of volatiles) and immediate protection under standard conditions[8] to yield the stable THP protected benzohydroximoyl chloride **5**. Chloride displacement using a variety of sodium alkoxides in dry DMF furnished the rearrangement substrates **2**. In general, rearrangements of **2** to **8** required 24 hr (xylenes, reflux) for high conversion. Deprotection under standard conditions[9] afforded the N-allylhydroxamic acids **9**.

For all substitution patterns present in the alkoxides that were examined, the chemistry proceeded uneventfully to provide products **8** (Table). One of the poorest yields for the sequence was realized during the chlorination/protection and we feel that this is due more to a technical problem than an inherent limitation of the chemistry. The instability of benzohydroximoyl chloride could be at the root of the problem, as manipulations more complicated than simple removal of volatiles gave even lower yields. When we

attempted to bypass workup of the chlorination, protection went awry leading to extensive decomposition.

An initial foray to extend this methodology to substrates other than the benzohydroximates described herein was successful. For example, subjection of cyclohexanecarboxaldehyde oxime to our protocol gave a reasonable yield of the corresponding protected hyroximoyl chloride, which underwent alkoxide displacements and subsequent rearrangement with the two allylic alcohols we attempted (entries g and h).

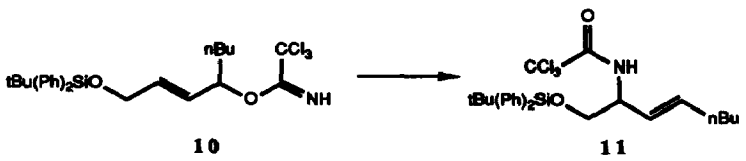
Table

						% yield*		
entry	R	R_1	R_2	R_3	R_4	2	8	9
a	Ph	H	H	H	H	60	68	75
b	Ph	Ph	H	H	H	53	60	87
c	Ph	Me	Me	H	H	45	70	86
d	Ph	H	H	Me	H	68	60	–
e	Ph	H	H	H	Me	53	89	–
f	Ph	Me	H	H	Me	46	45	–
g	Cy	Me	H	H	H	43	60	–
h	Cy	H	H	H	Me	18	60	–

* Yields refer to isolated products purified by column chromatography (SiO_2, hexanes:ethyl acetate). Satisfactory ^1H and ^{13}C NMR, mass spectra, IR spectra, UV spectra and elemental analysis have been obtained for these compounds.

The efficiency of chirality transfer in the [3,3]-rearrangement was addressed using nonracemic 3-penten-2-ol (entry f).[10] When this alcohol (97% e.e.[11a]) was carried through the sequence, the enantiomeric excess of the final product **8f** was significantly reduced (74% ee[11b]). While this result may limit the use of this rearrangement for the synthesis of enantiomerically pure products, incomplete transfer of chirality in such rearrangements is not unprecedented. In a recent example shown below (**10** → **11**), rearrangement under thermal conditions also led to incomplete chirality transfer.[12] These authors overcame the problem through the use of Pd catalysis ($Cl_2Pd(PPh_3)_2$) which facilitated efficient chirality transfer via rearrangement at lower temperature. Unfortunately, in our hands Pd catalysis was not effective. Nevertheless, our methodology can be used for the preparation of chiral N-allylhydroxamic acids and hydroxylamines of moderate enantiomeric purity.

Scheme 3



10 **11**

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