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Synthesis of Novel Cyclic Hydroxamic acids[#]

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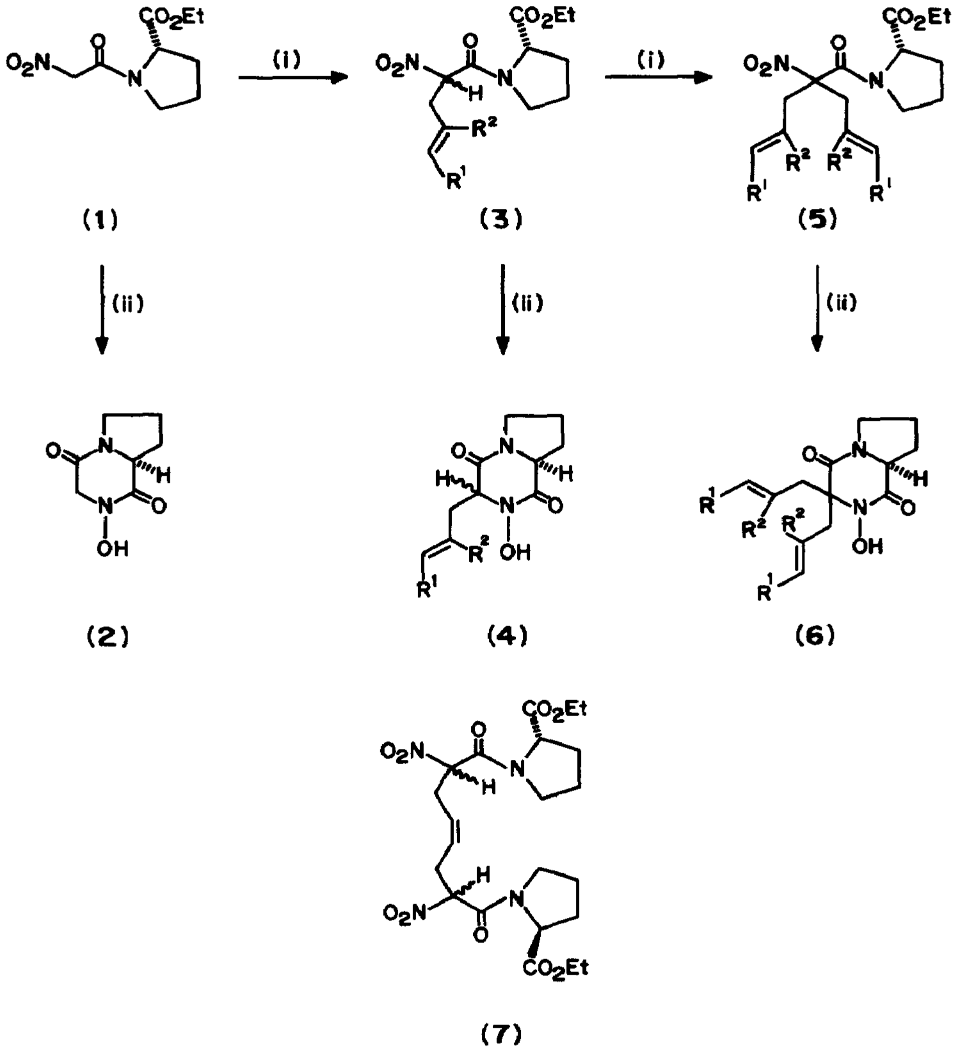
Abstract: *The nitroacetyl (S)-proline esters (1,3,5) are reduced by zinc-NH_4Cl to the hydroxylamine stage and cyclized to provide the novel chiral bicyclic hydroxamic acids (2,4,6). Michael addition of allyl acrylate on nitroacetic acid derivatives followed by Pd(0) catalyzed intramolecular allyl transfer and subsequent reduction of the nitro group yielded a novel class of cyclic hydroxamic acids related to pyroglutamic acid.*

Hydroxamic acids constitute an important class of siderophores, which play a major role in iron-solubilization and transport[1]. Some of these compounds have already found application as therapeutic agents, and the possibility of using them in drug delivery systems has been recently discussed[2]. In addition to their applications in medicine, it is expected that metal complexes of chiral hydroxamic acids may find use in selective DNA cleavage[3] and stereospecific epoxidation of allylic alcohols[4].

We now report a general synthesis of cyclic hydroxamic acids of wide applicability and demonstrate its use in the construction of several N-hydroxypyroglutamic acid derivatives as well as of chiral bicyclic 1-hydroxypiperazine-2,5-diones, formally derived from (S)-proline and N-hydroxyglycine. The synthesis is an extrapolation of our earlier work on the use of the nitroacetyl group as a peptide synthon[5], in which we had discovered i) a novel method of nitroacetylating *p*-and *sec*-amines, ii) mono- and bis- C-C bond formation on the reactive methylene by Pd(0)-catalysed allylation or Michael addition and iii) reduction of the NO_2 to NH_2 or NHAc. It struck us that at the terminal step, if the reduction were stopped at the hydroxylamine stage, ring closure on a suitably located carboxyl group would lead to novel hydroxamic acids.

Partial reduction of ethyl N-nitroacetyl-(S)-prolinate **1** by zinc dust in aqueous ethanolic NH_4Cl at 30°C, followed by refluxing in ethanol gave hydroxamic acid **2** in 85% yield. Its structure was confirmed by the intense violet color with $FeCl_3$, and the spectroscopic data[6]. The monoallyl (**4**) and bisallyl (**6**) derivatives were prepared similarly. Thus the nitro compound **3a** (mixture of diastereomers; *SS>RS; de=25%*) was subjected to partial reduction with Zn/aq.NH_4Cl/EtOH. The product **4a** was obtained in 80% yield as a gum. The nitroacetyl-(S)-proline ester with identical allyl substituents **5a** similarly gave the (S)-1-hydroxy-6,6-bis allylpiperazine-2,5-dione **6a** in 75% yield. The compounds **4b, 4c, 6b** and **6c** were prepared similarly. The Pd(0)-catalysed allylation of **1** with *cis*-1,4-butenediol diacetate gave **3d, 5d,** or **7** depending on the relative proportion of the two reactants. The α, α-bisallyl derivative **5d** was subjected to reduction under the above conditions to provide the 1-hydroxypiperazine-2,5-dione **6d** in 65% yield. The

SCHEME 1



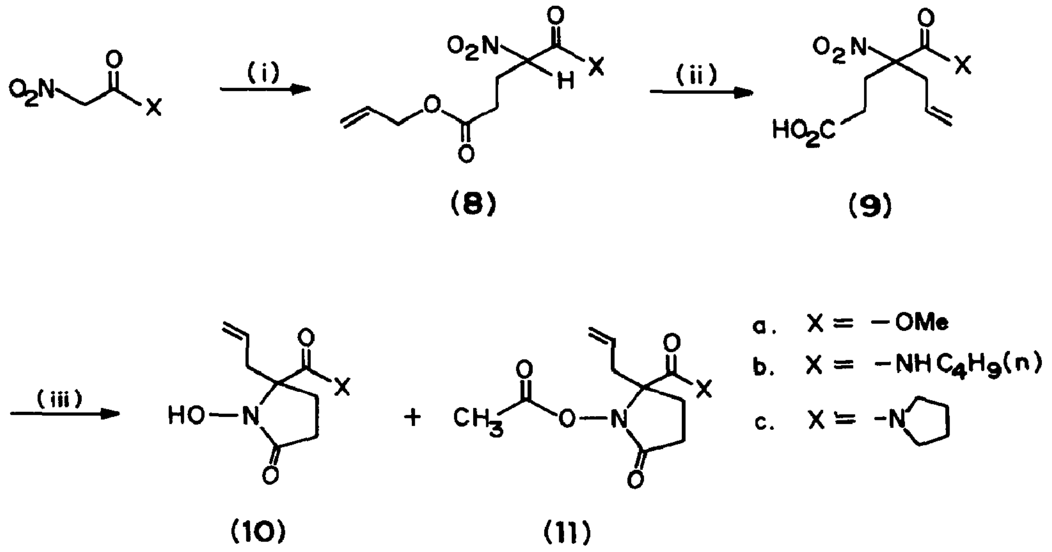
REAGENTS : (i) DBU, Pd$(dba)_2$, PPh_3, MeCN ; allyl acetate , 30°C

(ii) Zn, aq. NH_4Cl, EtOH ; Then reflux for 2-3h.

	R^1	R^2
a	H	H
b	Ph	H
c	H	Me
d	CH_2OAc	H

advantage of the above method consists in the fact that this provides access to 1-hydroxypiperazine-2,5-diones in which C-3 has a predetermined absolute configuration(*viz.,* S), while C-6 can carry 0,1 or 2 substituents (Scheme 1).

The synthesis of 5-membered cyclic hydroxamic acids related to pyroglutamic acid rested on the novel use of allyl acrylate as a Michael acceptor (Scheme 2). Addition of methyl nitroacetate to allyl acrylate gave the adduct (**8a**) in 85% yield. Treatment of this with the Pd(0) reagent in the presence of base led to the transfer of allyl group from oxygen to carbon, resulting in **9a**(63%). The presence of a quaternary carbon in this product was clearly shown by the ^{13}C NMR band at 94ppm. The intramolecular nature of this allylation was confirmed by carrying out the reaction in presence of added cinnamyl acetate, when the same product (**9a**) resulted; no trace of the corresponding cinnamyl derivative could be detected in the reaction product. Reductive acylation of the nitro group in (**9a**) led to the unexpected formation of the cyclic hydroxamic acid (**10a**) (55%) and its O-acetyl derivative (**11a**) (40%). The former gave the characteristic intense violet color with $FeCl_3$. It is presumed that the intermediate mixed anhydride is trapped by the incipient hydroxylamine, giving rise to (**10a**) by cyclization. Evidence for this was provided by the fact that a similar reduction of the corresponding ethyl ester (obtained in two steps from ethyl nitroacetate by Michael addition to ethyl acrylate



REACTION CONDITIONS : (i) KF/ TEBA , DMF , allyl acrylate , 30°C
(ii) Pd(dba)$_2$, PPh_3 , DBU , MeCN , 30°C
(iii) Zn , AcOH , Ac_2O , 60 – 75°C

followed by Pd(0) catalysed allylation) led to the acylamino derivative and not to the hydroxamic acid. A quaternary carbon was not essential for the cyclization to the hydroxamic acid. The adduct of ethyl nitroacetate with acrylic acid, on being subjected to reduction by $Zn/HOAc/Ac_2O$, gave the corresponding hydroxamic acid and its O-acetyl derivative. The synthesis is thus quite versatile[7]

The sequence of steps outlined above could be repeated with the appropriate precursor nitroacetic acid amides to give the hydroxamic acids (**10b**) and (**10c**) as well as their corresponding O-acetyl derivatives (**11b**) and (**11c**) in good yields. The importance of glutamic acid derivatives has been recently highlighted[8]. In this context our new procedure for the synthesis of N-hydroxypyroglutamic acids with a quaternary α-carbon assumes significance. We are currently studying the metal complexation properties of these compounds.

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\# NCL Contribution No. 5837

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6. All new compounds gave satisfactory elemental analysis.

7. We have extended this to nitroalkanes and nitrocycloalkanes. The results will be reported in the full paper.

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