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SYNTHESIS OF HYDROXAMIC ACIDS : $Pd/BaSO_4$ AS A NEW CATALYST FOR THE DEPROTECTION OF O-BENZYL HYDROXAMATES.

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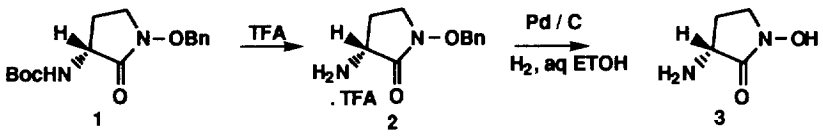
Summary : $Pd/BaSO_4$ was found to be an efficient catalyst in the deprotection of O-benzyl hydroxamates via hydrogenation to give the corresponding hydroxamic acids without further reduction to amides.

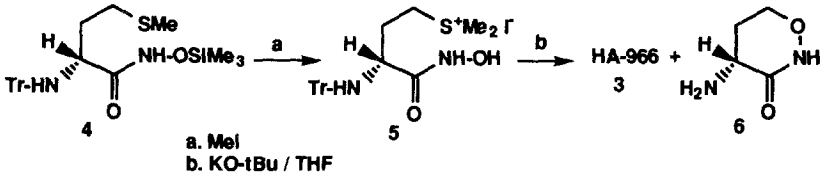
In recent years hydroxamic acid derivatives have received increasing attention due to their biological activity especially as enyzme inhibitors,[1] and metal chelators.[2a-f] The general method for the synthesis of these compounds is via the reaction of hydroxylamine with activated carboxylic acid derivatives. In cases where other reactive functionalities exist, O-protected hydroxylamine is coupled with the carboxylic acid followed by deprotection. Several methods exist for this transformation and have been well documented in the literature.[3] One of the preferred methods is via the reductive deprotection of O-benzylhydroxamates under catalytic hydrogenation conditions in the presence or absence of a base like pyridine.[3,4a,b] This route is attractive due to relatively mild reaction conditions and ease of workup. Our interest in this methodology was invoked initially during the synthesis of a potent N-methyl D-aspartate (NMDA) receptor antagonist HA-966 (**3**)[5-8] and later in the synthesis of a variety of hydroxamates as metalloprotease inhibitors.

The literature processes for the synthesis of HA-966 involved the hydrogenation of the TFA salt of O-benzyl hydroxamate intermediate (**2**)[5] in the presence of Pd/C,[6] Pearlman's catalyst,[7] or Pd black [8] (Scheme 1). Alternatively O-TMS derivative **4** was synthesized and deprotected to give intermediate **5** (Scheme 2) which was penultimately cyclized to give the desired HA-966 (**3**) and the undesired by-product (**6**)[9] in 20:1 ratio.

Scheme 1

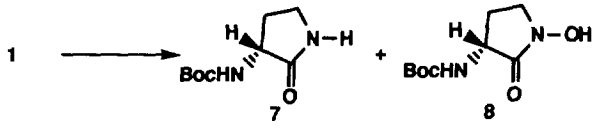


Scheme 2



For our synthetic purposes we required Boc-protected hydroxamic acid derivative **8** and HA-966 (**3**) itself. In our hands the deprotection of the TFA salt of O-benzyl hydroxamate (**2**) gave us the desired HA-966 (**3**) as reported,[5,7] however similar debenzylation of the intermediate **1** did not take place cleanly and invariably a mixture of the desired product (**8**) and the amide (**7**) was obtained (Scheme 3). Variations of the catalyst viz. Pd/C (5%, 10%, 20%), Pd black and $Pd/SrCO_3$ (10%)[10] and pressure (10-50psi) did not give the desired product cleanly. With more reactive catalysts (Pd/C, 10% and 20%) only the amide could be isolated and with $Pd/SrCO_3$ starting material (**1**) was recovered. This prompted us to use $Pd/BaSO_4$ (10%)[11] as the catalyst for the hydrogenation. Only the desired hydroxamic acid derivative (**8**) was isolated in 72% yield after crystallization. Other reagents including TMS-I or BBr_3[12] or catalytic hydrogenation (Pd/C, 5, 10 or 20%) in the presence of pyridine gave mixtures. The synthesis of **8** could be carried out consistently in several different experiments in around 70% isolated yield without any amide (**7**) formation.[13]

Scheme 3



In another project we had a need for several peptidic hydroxamic acids as metalloprotease inhibitors. We used the method described above to deprotect the benzyloxy hydroxamate intermediates cleanly without the formation of corresponding amide impurities, which were observed with Pd/C as a catalyst. Pd / $BaSO_4$ (5%) was successfully used as a catalyst for hydrogenation to give the corresponding hydroxamic acids (Scheme 4). In a typical experiment the O-benzyl hydroxamate[14] was dissolved in methanol and hydrogenated (H_2, 50psi) using Pd / $BaSO_4$ (5%) as the catalyst. The reaction mixture was filtered and the filtrate was evaporated to give the desired product in good to excellent yields after purification. Various hydroxamic acids synthesized are listed in Table 1. Debenzylation of O-benzyl hydroxamate (entry #4, Table 1) with Pd/C (5%) gave mainly the corresponding amide as the product.[15]

Scheme 4

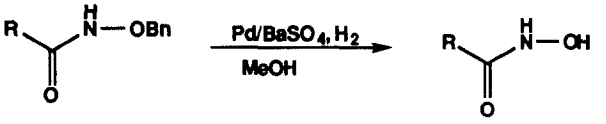


Table 1. Peptidic hydroxamic acid derivatives synthesized via the hydrogenolysis of O-benzylhydroxamates in the presence of Pd / $BaSO_4$.

	Hydroxamate	Yield (%)*
1	Boc-Ile-Trp-NHOH	51
2	N-Azepinoyl-Ile-Trp-NHOH	74
3	N-Azepinoyl-Leu-Trp-NHOH	58
4	Boc-Ile-Ile-Trp-NHOH	85
5	Boc-Ile-Ile-(D)Trp-NHOH	64
6	$HO_2C(CH_2)_2$-C(O)-Ile-Ile-Trp-NHOH	70
7	$NH_2(CH_2)_{10}$-C(O)-Ile-Ile-Trp-NHOH	69
8	$MeO_2C(CH_2)_3$-C(O)-Trp-NHOH	86
9	Boc-Asp-Ile-Ile-Trp(CHO)-NHOH	98
10	Ile-Ile-Pro-NHOH	68
11	HOHN-C(O)-$(CH_2)_2$-C(O)-Trp	78
12	HOHN-C(O)-$(CH_2)_3$-C(O)-Trp	91

* compounds were purified by column chromatography and gave satisfactory H-NMR, MS and elemental analysis.

In conclusion, we have developed an efficient general method for the deprotection of benzyloxy hydroxamates via catalytic hydrogenation using Pd/$BaSO_4$ as a catalyst to give the corresponding hydroxamic acids in good to excellent yields.

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5. Intermediate **2** was in turn obtained from (3R)-3-t-butoxycarbonyl-amino-1-benzyloxypyrrolidin-one (**1**). Compound **1** was synthesized starting from Boc-D-methionine in 2 steps.[8a-b]
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11. Pd/$BaSO_4$ (10%) was prepared in our high pressure laboratory using $BaSO_4$ (90g), $PdCl_2$ (60%, 16.7g) and $LiOH.H_2O$ (7.9g) in water. The deprotection worked equally well with Pd/$BaSO_4$ (5%) obtained from Johnson Mattey.
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13. Compound 1 (35.49g, 116mmol) in methanol (1000ml) was hydrogenated (H_2, 50 psi) in the presence of 10% Pd/$BaSO_4$ (2.5g, Johnson Mathey, cat. # 21162). Reaction was monitored by HPLC. On completion the reaction mixture was filtered and filtrate evaporated to dryness. The solid obtained was triturated with pet. ether : ethyl acetate (2:8) to give buff product. 18.17g = 72.5%. IR, ^{1}HNMR and MS were in agreement with the structure and elemental analysis was calculated for $C_9H_{16}N_2O_4$, C, 49.99; H, 7.46; N, 12.95; Found C, 50.34; H, 7.50; N, 12.78. $[\alpha]_D = 41.2°$ (c, 1.038, MeOH).
14. The intermediate N-benzyloxy hydroxamates were synthesized by coupling the corresponding carboxylic acid derivatives with benzylhydroxylamine in the presence of couplings agents like DCC or EDAC (ethyl-3-(3-dimethylamino)-propyl-carbodimide) in DMF.
15. Boc-Ile-Ile-Trp-NHOBn (50mg, 0.079mmol) was hydrogenated (H_2, 50psi) using Pd/C(5%, 30mg) as the cataslyst. No conversion to the hydroxamic acid was observed after 22h. Additional catalyst (45mg and 35mg) was added at 22h interval. After the second addition no starting material was seen (HPLC, C-18, Vyadec, H_2O-AcCN-0.1%TFA, 9:1-1:1 gradient). On evaporation of the filtrate only the corresponding amide was isolated, which was characterized by ^{1}H-NMR and MS(FAB) : M+1 = 530.

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