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TITANIUM (III) MEDIATED SYNTHESIS OF DICARBOXYPYRAZINES

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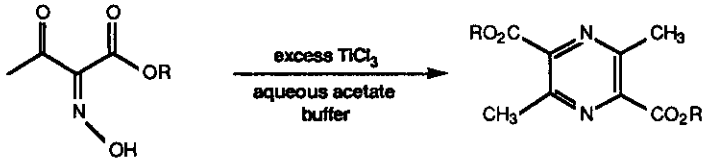
Abstract-Titanium (III) induced reductions of α-hydroxyimino-ß-ketoesters lead to the formation of tetrasubstituted pyrazines.

One of the classical methods for the formation of pyrazines is through the formation of α-amino carbonyl compounds which dimerize and subsequently aromatize to give the corresponding pyrazine. Oximes have often been used as latent functionalities in this regard through their conversion to the corresponding amine by a variety of reductive processes.[1] Carboxypyrazines have been formed via this method, most recently by catalytic hydrogenation.[2]

In the course of our studies on the synthesis and reduction of nitrogen bearing compounds, we observed that when oxime **1a**[3] was reduced with excess aqueous $TiCl_3$, a white solid was isolated which we subsequently identified as pyrazine **2a**.[4] To our knowledge, Ti(III) has never been used to reduce α-hydroxyimino-carbonyls for the purpose of pyrazine formation. Normally oximes (hydroxyimines) react with Ti(III) to generate carbonyl compounds which are the result of hydrolysis of intermediate imines.[5] Pyrazine formation is surprizing in that, instead of imine formation and hydrolysis, another reactive pathway dominates. There appear to be many mechanistic pathways which could account for pyrazine formation (SCHEME I). Although reduction of **1** to the imine **3** and subsequent

(1)

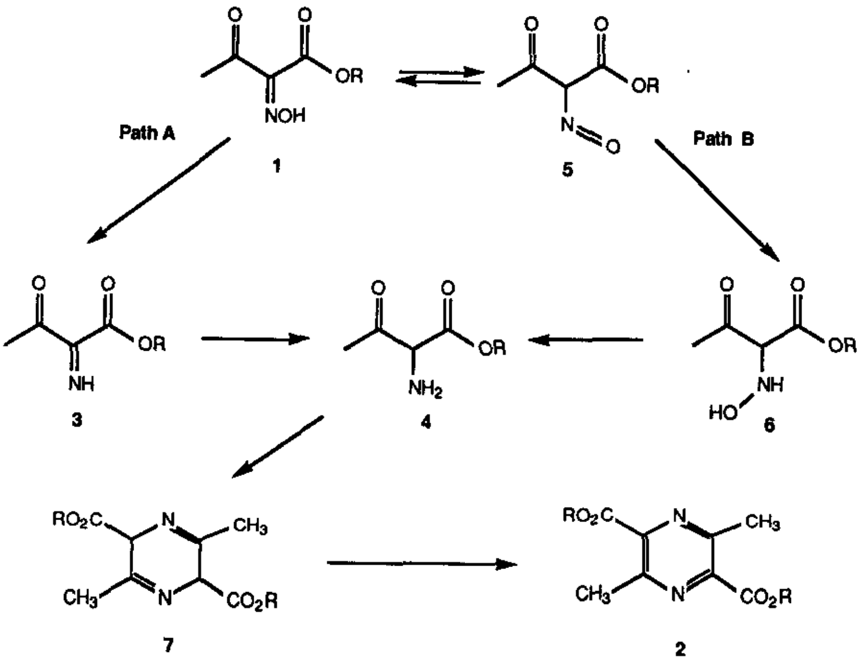


1

a) R = t-Bu
b) R = CH_3

2

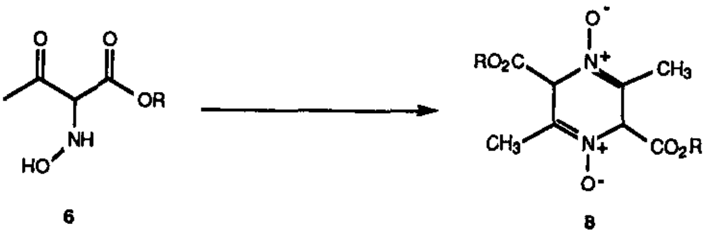
a) R = t-Bu
b) R = CH_3



Scheme I

reduction to the amine **4** cannot be eliminated, it is by no means the only possible mechanism. Reduction of the tautomeric nitroso compound **5** would result in the production of hydroxylamine **6**. Further reduction to the amine **4** would again provide the known α-amino-β-ketoester precursors of pyrazines.[2] This would appear to be reasonable, since the reduction of nitro arenes to aryl amines with Ti(III) is a known process,[6] and is postulated to proceed through nitroso and hydroxylamine intermediates. It would also seem reasonable that the

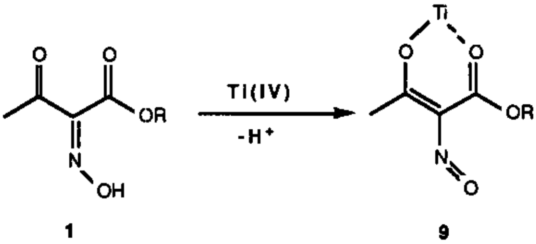
(2)



intermediate hydroxylamine **6** could dimerize to form a subsequent intermediate dinitrone **8**. Reduction and aromatization would result in the formation of the observed pyrazine product. McMurry interprets the Ti(III) mediated production of a cyclic imine to be the result of an intramolecular reaction of a nitroso compound with a carbonyl followed by Ti(III) induced reductions.[7] This possibility must also be considered, particularly in light of the carbonyl coupling chemistry he subsequently reported.[8]

The reduction was initially carried out in a buffered aqueous environment at pH 7. The apparent pKa of oxime **1a**, as determined by acid titration in a mixed H_2O:DMF (3:1) solvent system, is 7.5. Therefore, there is a significant amount of anionic

(3)



character present in the molecule. The aqueous $TiCl_3$ solution we used in this study (purchased from Aldrich) contains an appreciable amount of Ti(IV). It is known that anions of acetoacetates chelate strongly with Ti(IV).[9] This suggests that the nitroso form of the starting material, as the anion **9**, may be the reactive species. In support of this possibility, we have observed that when **1a** is subjected to excess $TiCl_3$ at pH 9, the recrystallized yield of **2a** was 52%, whereas at pH 5 no pyrazine product was isolated. We have also been able to isolate **2b**[2] from **1b** in a 30% recrystallized yield at pH 7, while no pyrazine was isolated at pH 5. The reactions were performed using the following general procedure under an argon atmosphere. To a solution of 15 ml of water containing 60 mmole of sodium acetate was added approximately 6 mmole of aqueous $TiCl_3$. The solution was adjusted to the desired pH with 50% NaOH. The oxime (1 mmole) was dissolved in 2 ml of methanol and added quickly to the titanium solution. After stirring under an argon atmosphere for 3 h the flask was opened to the air and allowed to stir until the solution was completely white. After adjusting the aqueous layer to pH 9, it was extracted 3 times with CH_2Cl_2. The organic layers were combined, washed with brine, dried over $MgSO_4$, and evaporated to yield a yellowish oil which eventually solidified. The solid was recrystallized from ethanol to yield the appropriate carboxypyrazine. Though these unoptimized yields are not spectacular, nor is the mechanism of this reaction clarified, this method provides a unique means of access to the dicarboxypyrazine skeleton.

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4. Characterization data for **IVa**: mp 133-134°C; ^{1}H NMR ($CDCl_3$) δ 1.68 (s,3H), 2.73 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.02,28.17,83.51,145.43,149.29,164.69; IR (KBr) 1730 cm^{-1}. Anal. calcd. for $C_{16}H_{24}N_2O_4$: C(62.30), H(7.85), N(9.09). Found: C(62.09), H(7.92), N(8.96).
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