

Preparation of quinoxalines, dihydropyrazines, pyrazines and piperazines using tandem oxidation processes

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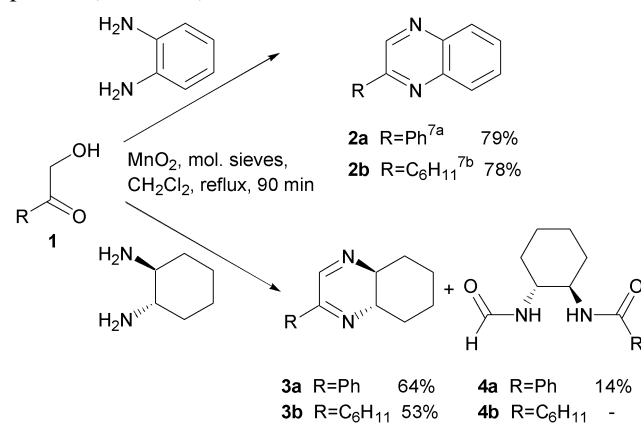
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α -Hydroxyketones undergo MnO_2 -mediated oxidation followed by *in situ* trapping with aromatic or aliphatic 1,2-diamines to give quinoxalines or dihydropyrazines, respectively, in a one pot procedure which avoids the need to isolate the highly reactive 1,2-dicarbonyl intermediates. Modifications of the procedure allow the formation of pyrazines and piperazines.

Quinoxalines constitute the basis of many insecticides, fungicides, herbicides and anthelmintics, as well as being important in human health and as receptor antagonists.^{1,2} Dihydropyrazines, piperazines and pyrazines are also of great importance in natural products and chemotherapeutic agents.^{2a,3}

We have recently developed a number of manganese dioxide-based tandem oxidation processes (TOPs) for the elaboration of alcohols.⁴⁻⁶ As part of this programme, we discovered an *in situ* oxidation-amine trapping process leading to imines.⁵ In addition, we recently established that α -hydroxyketones undergo *in situ* oxidation-trapping when treated with manganese dioxide in the presence of stabilised Wittig reagents.⁶ We therefore decided to investigate the conversion of α -hydroxyketones **1** into quinoxalines **2** or dihydropyrazines **3** by the use of manganese dioxide along with suitable 1,2-diamino compounds (Scheme 1).



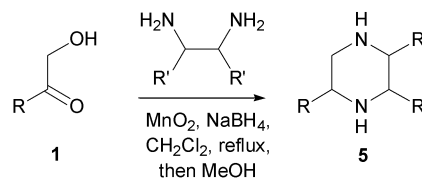
Scheme 1 Formation of quinoxalines and dihydropyrazines.^{8,9}

We have shown these processes to be effective for a range of α -hydroxyketones **1** and 1,2-diamines (Scheme 1).¹⁰ The dihydropyrazines **3** were sometimes accompanied by *N*-acyl-*N'*-formyl-*trans*-1,2-diaminocyclohexane byproducts **4**. There is an isolated example of the oxidative cleavage of bis-hemiaminals¹¹ and we propose a similar MnO_2 -mediated process leading to **4**.¹²

Having shown that it is possible to produce dihydropyrazines **3** *in situ* using TOP methodology, attention moved to extended one-pot procedures. We recently reported the production of secondary and tertiary amines from activated alcohols using a MnO_2 mediated one-pot oxidation imine-formation reduction sequence.⁵ We envisaged a similar sequence leading from α -hydroxyketones **1** to piperazines **5** (Scheme 2). Thus, the dihydropyrazine-forming reactions described above were repeated using $\text{MnO}_2/\text{NaBH}_4$. No piperazine formation was

observed under these conditions, but the addition of excess methanol to the reaction mixture after dihydropyrazine formation gave the corresponding piperazines **5a-f** in good yields (Table 1).

As can be seen (Table 1), the procedure gave good to excellent yields with aromatic (entries i-iii) and aliphatic (entries iv-vi) α -hydroxyketones. In the reactions using (\pm)-*trans*-1,2-diaminocyclohexane (entries ii-iv, vi), only one



Scheme 2 *In situ* formation of piperazines.¹³

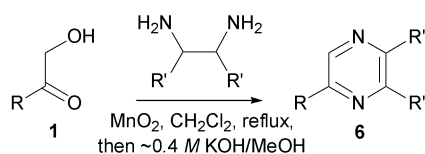
Table 1 *In situ* piperazine formation¹³

	R	R'	Piperazine 5	Yield ^a (%)
i	Ph	H	5a	52
ii	Ph	(CH ₂) ₄	5b	75
iii	2-Fur	(CH ₂) ₄	5c	60 ^b
iv	C ₆ H ₁₁	(CH ₂) ₄	5d	84
v	Hydrocortisone	H	5e	69
vi	Hydrocortisone	(CH ₂) ₄	5f	87 ^c

^a Yields refer to chromatographically pure product.⁹ ^b Compound **5c** proved sensitive to acid/base extraction; it was therefore isolated as the corresponding diacetate. ^c Formed as a mixture (*ca.* 1 : 1) of diastereomers.





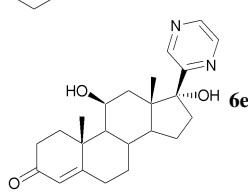
diastereomeric product was isolated and we have tentatively assigned these as the all-equatorial adducts shown.¹⁴

Finally, we investigated a TOP-aromatisation sequence leading to pyrazines **6**. To this end, the original dihydropyrazine formation was repeated in THF and toluene at extended reflux in the presence of excess MnO₂ in order to effect the aromatisation. However, under these conditions, only trace amounts of pyrazines **6** were observed in the toluene reaction. The use of co-oxidants, such as DDQ and CAN, in these reactions resulted in complete degradation of the dihydropyrazines **5**. We eventually established that the addition of ~0.4 M KOH in methanol¹⁵ to the refluxing reaction mixture after the formation of dihydropyrazines **5** resulted in production of the corresponding pyrazines **6** (Scheme 3). It should be noted that the addition of methanol alone did not achieve the desired transformation. The results are summarised in Table 2. As is apparent, the presence of an aromatic substituent facilitates aromatisation.



Scheme 3 *In situ* formation of pyrazines.¹⁶

Table 2 *In situ* pyrazine formation¹⁶

R	R'	Pyrazine 6	Yield ^a (%)
i	Ph	 6a ^{17a}	45
ii	Ph	 6b	66
iii	2-Fur	 6c	64
iv	C ₆ H ₁₁	 6d ^{17b}	33
v	Hydrocortisone	 6e	10

^a Yields refer to chromatographically pure product.⁹

In conclusion, we have developed novel methodology for the conversion of α -hydroxyketones **1** into the corresponding quinoxalines **2** and dihydropyrazines **3** via a tandem oxidation procedure with *in situ* trapping using 1,2-diamines. This methodology has been successfully extended to allow the direct, one-pot conversion of the dihydropyrazines into the corresponding piperazines and pyrazines in fair to good yields. Further work is continuing to optimise and apply this new chemistry.

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- Piperazines: As described in ref. 8 but diamine reduced to 0.60 mmol and NaBH₄ (0.076 g, 2.00 mmol) included. After complete consumption of substrate, MeOH (6 mL) added at RT and stirred for 20 h. Work up and purification by acid/base extraction gave the desired product.
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- Pyrazines: As described in ref. 8 but after consumption of substrate, ~0.4 M KOH in MeOH (5 mL) added and reflux continued for 20 h. Work up and purification by flash column chromatography on silica gave the desired product.
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