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

Steven A. Raw, Cecilia D. Wilfred and Richard J. K. Taylor*

Department of Chemistry, University of York, Heslington, York, UK YO10 5DD. E-mail: rjkt1@york.ac.uk; Fax: +44(0)1904 434523; Tel: +44(0)1904 432606

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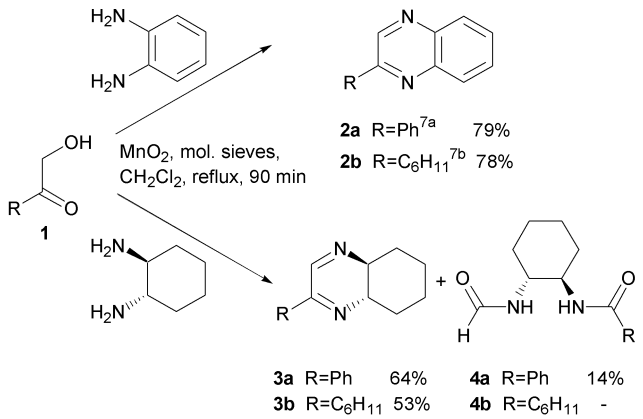
α-Hydroxyketones undergo MnO_2-mediated oxidation followed by *in situ* trapping with aromatic or aliphatic 1,2-diamines to give quinoxalines or dihydropyrazines, respectively, in a one pot procedure which avoids the need to isolate the highly reactive 1,2-dicarbonyl intermediates. Modifications of the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

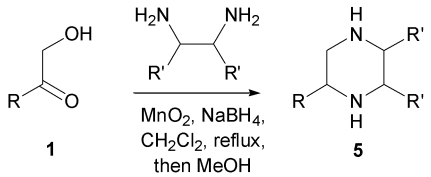


Scheme 1 Formation of quinoxalines and dihydropyrazines.[8,9]

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-hemiaminals[11] 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 MnO_2/$NaBH_4$. 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 (±)-*trans*-1,2-diaminocyclohexane (entries ii–iv, vi), only one



Scheme 2 *In situ* formation of piperazines.[13]

Table 1 *In situ* piperazine formation[13]

	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_6H_{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.

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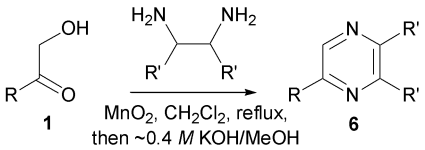
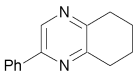
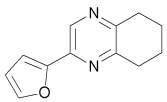
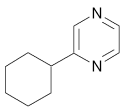
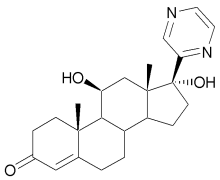
diastereomeric product was isolated and we have tentatively assigned these as the all-equatorial adducts shown.[14]

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 MnO_2 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 methanol[15] 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 formation[16]

	R	R′	Pyrazine **6**	Yield[a] (%)
i	Ph	H	 **6a**[17a]	45
ii	Ph	$(CH_2)_4$	 **6b**	66
iii	2-Fur	$(CH_2)_4$	 **6c**	64
iv	C_6H_{11}	H	 **6d**[17b]	33
v	Hydrocortisone	H	 **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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8 General procedure for quinoxalines and dihydropyrazines: To a mixture of α-hydroxyketone (0.50 mmol), 1,2-diamine (1.00 mmol) and powdered 4 Å molecular sieves (0.50 g) in dry CH_2Cl_2 (25 mL) was added activated MnO_2 (0.435 g, 5.00 mmol) and the mixture heated to reflux. With ethylenediamine, 2.0 M HCl in Et_2O (1 eq. w.r.t. amine) was also added to suppress formation of **4**. After complete reaction, the mixture was cooled to RT, filtered through Celite® and the residue washed well with CH_2Cl_2. Concentration and purification of the crude product by flash column chromatography on silica for quinoxalines or deactivated, neutral alumina for dihydropyrazines gave the desired product displaying consistent spectral data.

9 Known compounds gave data consistent with those published: novel compounds were fully characterised.

10 Additional examples will be described in a full paper.

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13 Piperazines: As described in ref. 8 but diamine reduced to 0.60 mmol and $NaBH_4$ (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.

14 For precedent see K. Gollnick, S. Koegler and D. Maurer, *J. Org. Chem.*, 1992, **57**, 229; L. W. Jenneskens, J. Mahy, E. M. M. de Brabander-van den Berg, I. Van der Hoef and J. Lugtenburg, *Recl. Trav. Chim. Pays-Bas*, 1995, **114**, 97. Furthermore, the pertinent coupling constants in the ^{1}H NMR spectra of these compounds were in the range indicative of *trans*-diaxial protons.

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16 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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