Chromium-Assisted Oxidations:[1] A Simple and Efficient Oxidation of Oxazolopyridylcarbinols by Aqueous *tert*-Butyl Hydroperoxide

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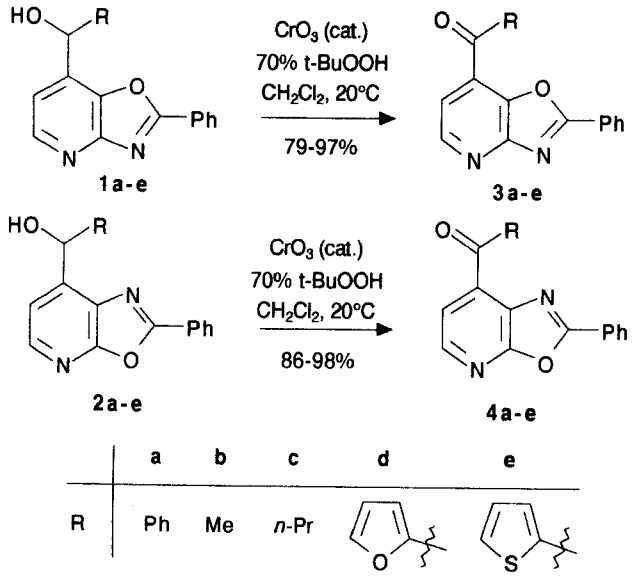
The oxidation of oxazolopyridylcarbinols to the corresponding ketones has been carried out in high yields using commercial aqueous 70% *tert*-butyl hydroperoxide and catalytic amounts of chromium(VI) oxide.

Oxazolo[4,5-*b*]pyridines and -[5,4-*b*]pyridines constitute an important group of compounds due to their biological properties. Their activities depend mainly on the nature of the substituents on the basic heterocyclic framework.[2] For example, some oxazolopyridyl ketones exhibit analgesic properties.[3] They have been precedently obtained directly by homolytic acylation of 2-phenyloxazolo[4,5-*b*] or -[5,4-*b*]pyridines[4] or by oxidation of the corresponding alcohols using manganese dioxide in refluxing toluene.[5] As large excesses of this oxidant are required, the workup leads to considerable amounts of waste material. Building upon our earlier findings,[6,7] we considered a catalytic procedure as an alternative approach. We are pleased to report that the oxidation of oxazolopyridylcarbinols **1** and **2**[5] to the corresponding ketones can be efficiently carried out by *tert*-butyl hydroperoxide in the presence of catalytic amounts of chromium(VI) oxide.



Preliminary experiments performed under conditions used for the oxidation of arylcarbinols[7] afforded the expected ketone with high selectivity but with incomplete consumption of the substrate. For example, the oxidation of **1a** using CrO_3 (0.05 equiv), aqueous 70% *t*-BuOOH (4 equiv) and dichloromethane as solvent led after 24 hours to a 44% yield of **3a** with recovery of 50% of the starting alcohol. The conversion was not modified if the reaction time was increased. This latter observation was expected since we noted that the red-purple colour of the inital mixture was bleached after one day indicating the decay of the oxidizing species.[8]

Next, the reaction was repeated except that new portions of both CrO_3 (0.05 equiv) and *t*-BuOOH (4 equiv) were added to the mixture after 24 hours and stirring was continued for one day. With these experimental modifications, **3a** was isolated in 93% yield and the consumption of **1a** was 98%. Thus, the oxidation of **1b–e** and **2a–e** was carried out using this procedure. As attested by the results listed in the Table, high yields were uniformly obtained. Furthermore, it is interesting to note that the furyl ring[9] and S and N heteroatoms[10] were unaffected under these conditions.

Table. Oxidation of **1** and **2** with CrO_3 (0.05 equiv × 2) and 70% *t*-BuOOH (4 equiv × 2) in dichloromethane at room temperature

Alcohol	Time (h)	Conversion (%)	Ketone, Yield (%)[a,b]	Ketone, mp °C (Lit.[5])
1a	24 × 2	98	**3a**, 93	135 (135–136)
1b	22 × 2	81	**3b**, 79	156–158
1c	12 × 2	86	**3c**, 85	110–111 (111–112)
1d	24 × 2	> 98	**3d**, 97	179–180
1e	24 × 2	> 98	**3e**, 97	147–148
2a	24 × 2	98	**4a**, 97	170 (172–173)
2b	22 × 2	90	**4b**, 86	125–126
2c	12 × 2	89	**4c**, 88	86 (85–86)
2d	24 × 2	98	**4d**, 89	176–177
2e	24 × 2	> 98	**4e**, 98	174–175

[a] Isolated yields calculated on the amount of alcohol introduced.
[b] All new compounds gave satisfactory microanalysis C ± 0.32, H ± 0.16, N ± 0.24 or HRMS ± 0.0016 amu.

In conclusion, it appears that the CrO_3/*t*-BuOOH system constitutes a very simple and mild method to carry out the oxidation of oxazolopyridylcarbinols even in the presence of a thienyl group.

Starting alcohols were obtained by functionalization at the 7-position of 2-phenyloxazolo[4,5-*b*] or -[5,4-*b*]pyridines with aldehydes.[5] ^{1}H NMR spectra were recorded in $CDCl_3$ as solvent on a AC 250 Bruker instrument and are referenced in δ (ppm) to tetramethylsilane as the internal standard. IR spectra were obtained in $CHCl_3$ as solvent on a SP 3.300 Philips spectrophotometer. Melting points were determined on a Büchi apparatus and elemental analysis on a CHN 2400 Perkin-Elmer. High resolution mass spectrometry was

carried out on a VG Analytical 70-S instrument. Compounds **3a**, **3c**, **4a** and **4c** have already been described.[5]

Oxidation of Oxazolopyridylcarbinols; General Procedure:
All reactions were carried out at r.t. under an air atmosphere. In a round-bottom flask containing a stirred mixture of CrO_3 (0.05 equiv) in CH_2Cl_2 (25 mL/mmol) was added sequentially commercial aqueous 70% *t*-BuOOH (4 equiv) and alcohol. When the colour of the mixture became yellow (12 to 24 h, see Table), new portions of CrO_3 (0.05 equiv) and 70% *t*-BuOOH (4 equiv) were added. The stirring was maintained for 12 to 24 h (see Table); then, the mixture was filtrated on a pad of alumina. After evaporation of solvents, the crude product was purified by chromatography on silica gel.

Caution: For large scale experiments, it is necessary to carry out a workup with a reducing aqueous solution to remove residual peroxides (Na_2SO_3/H_2O for example, see conditions referenced in[11]).

7-Acetyl-2-phenyloxazolo[4,5-b]pyridine (**3b**):
IR: $\nu = 1680\ cm^{-1}$.
^1H NMR: $\delta = 2.95$ (s, 3H), 7.55–7.65 (m, 3H), 7.72 (d, 1H, $J = 5$ Hz), 8.35 (dd, 2H, $J = 8$, 1.5 Hz), 8.7 (d, 1H, $J = 5$ Hz).

7-(2-Furylcarbonyl)-2-phenyloxazolo[4,5-b]pyridine (**3d**):
IR: $\nu = 1640\ cm^{-1}$.
^1H NMR: $\delta = 6.72$ (dd, 1H, $J = 3.5$, 1.6 Hz), 7.42 (d, 1H, $J = 3.5$ Hz), 7.5–7.65 (m, 3H), 7.67 (d, 1H, $J = 5$ Hz), 7.80 (d, 1H, $J = 1.6$ Hz), 8.30 (dd, 2H, $J = 8$, 1.5 Hz), 8.75 (d, 1H, $J = 5$ Hz).

7-(2-Thienylcarbonyl)-2-phenyloxazolo[4,5-b]pyridine (**3e**):
IR: $\nu = 1630\ cm^{-1}$.
^1H NMR: $\delta = 7.22$ (dd, 1H, $J = 5$, 4 Hz), 7.5–7.65 (m, 4H), 7.72 (dd, 1H, $J = 4$, 1.1 Hz), 7.88 (dd, 1H, $J = 5$, 1.1 Hz), 8.30 (dd, 2H, $J = 8.4$, 1.4 Hz), 8.75 (d, 1H, $J = 5$ Hz).

7-Acetyl-2-phenyloxazolo[5,4-b]pyridine (**4b**):
IR: $\nu = 1680\ cm^{-1}$.
^1H NMR: $\delta = 3.05$ (s, 3H), 7.55–7.65 (m, 3H), 7.80 (d, 1H, $J = 5$ Hz), 8.35 (dd, 2H, $J = 8$, 1.5 Hz), 8.45 (d, 1H, $J = 5$ Hz).

7-(2-Furylcarbonyl)-2-phenyloxazolo[5,4-b]pyridine (**4d**):
IR: $\nu = 1650\ cm^{-1}$.
^1H NMR: $\delta = 6.65$ (dd, 1H, $J = 3.5$, 1.7 Hz), 7.42 (d, 1H, $J = 3.5$ Hz), 7.5–7.62 (m, 3H), 7.65 (d, 1H, $J = 5.3$ Hz), 7.77 (d, 1H, $J = 1.7$ Hz), 8.3 (dd, 2H, $J = 7.2$, 1.5 Hz), 8.50 (d, 1H, $J = 5.3$ Hz).

7-(2-Thienylcarbonyl)-2-phenyloxazolo[5,4-b]pyridine (**4e**):
IR: $\nu = 1630\ cm^{-1}$.
^1H NMR: $\delta = 7.18$ (dd, 1H, $J = 5$, 4 Hz), 7.5–7.65 (m, 4H), 7.72 (br d, 1H, $J = 4$ Hz), 7.88 (br d, 1H, $J = 5$ Hz), 8.3 (br d, 2H, $J = 7$ Hz), 8.48 (d, 1H, $J = 5$ Hz).

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