A New Protocol for the Conversion of Isoxazolidines to 1,3-Amino Alcohols

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A number of fused-ring isoxazolidines **3** have been successfully transformed into the corresponding 1,3-amino alcohols **5** through oxidation with 3-chloroperbenzoic acid and subsequent catalytic hydrogenation.

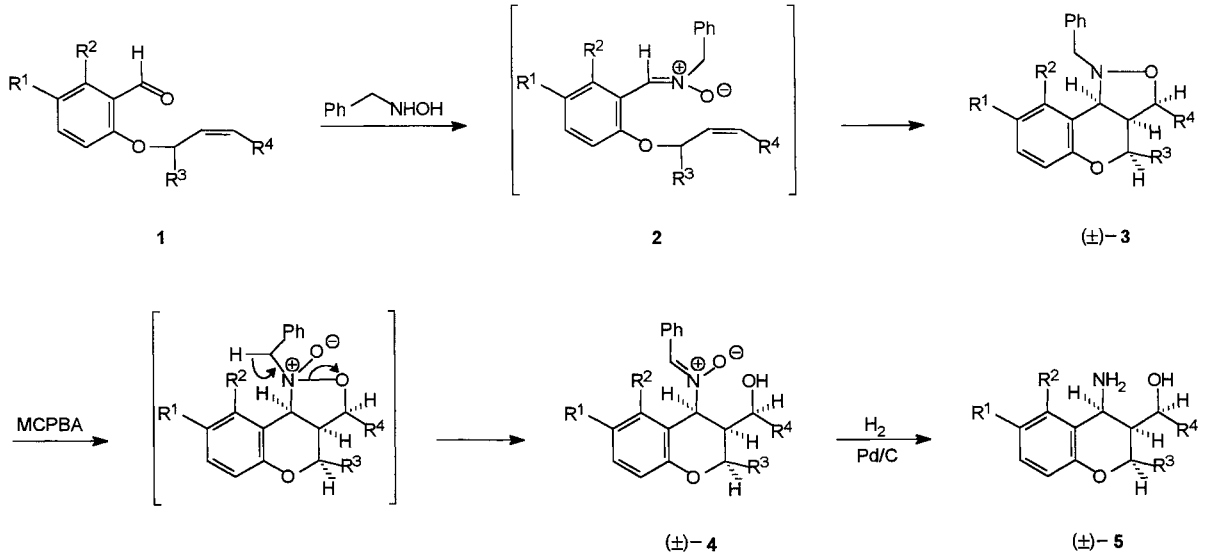
The so-called cycloadditive route to 1,3-amino alcohols was discovered some time ago and later showed a wide variety of applications.[1] The cleavage of the N–O bond of the first-formed isoxazolidines occurs under reductive conditions.[1,2] The catalytic hydrogenation is greatly advantageous with respect to other procedures whenever one must remove a benzyl-like *N*-substituent which has been previously introduced as protective group (the benzyl itself) or as chiral auxiliary (e.g. α-methylbenzyl). However, this procedure can preclude the preparation of 1,3-amino alcohols having the amine functionality in the benzylic position. Such a drawback has been encountered by us within a framework of research aimed at the preparation of 4-amino-3-(hydroxymethyl)chromans.[3] In this context, we have now developed a new protocol for the conversion of isoxazolidines to 1,3-amino alcohols.

We first synthesized the unreported fused-ring isoxazolidines **3** by intramolecular cycloaddition of the transient species **2**, generated in situ by reaction of the properly substituted aldehydes **1** with benzylhydroxylamine (Scheme, Table). The stereochemical outcome of the cycloaddition, namely the *cis* junction between the condensed rings, parallels the previously reported trend.[3–6]

Treatment of compounds **3** with 3-chloroperbenzoic acid (MCPBA) resulted in the nitrone derivatives **4**, the formation of which can be explained in terms of *N*-oxidation of the isoxazolidine moiety followed by heterolytic ring cleavage and concomitant prototropic shift (Table). The reaction of isoxazolidines with peroxy acids has some precedents in the chemical literature,[7–11] but in our opinion the potential of this reaction is far from thoroughly exploited. The full selectivity observed about the proton migration may be the consequence of the required coplanarity between the C–H and N–O bonds being broken.

Compounds **4** underwent catalytic hydrogenation in the presence of Pd/C to give the desired amino alcohols **5** (Scheme, Table). Significantly, the direct hydrogenation of the cycloadducts **3** led to 4-unsubstituted 3-(hydroxymethyl)chromans.

Melting points were determined on a Büchi apparatus and are uncorrected. IR spectra were recorded on a FT-IR Perkin Elmer 1725 X spectrophotometer. ^{1}H NMR spectra were obtained on a



1 **2** (±)-**3** (±)-**4** (±)-**5**

Entry	R^1	R^2	R^3	R^4
a	H	H	H	H
b	$(-CH=CH-)_2$		H	H
c	H	H	$(-CH_2-)_3$	
d	F	H	$(-CH_2-)_3$	

Scheme

Table. Compounds **3–5** Prepared

Product[a]	Time (h)	Yield[b] (%)	mp (°C)[c]	^{1}H NMR ($CDCl_3$/TMS) δ, J (Hz)	MS (70 eV) m/z (M^+)	IR (Nujol) ν (cm^{-1})
3a	3	87	120–121	3.03–3.14 (1H, m), 3.82 (1H, dd, J = 4.7, 8.2), 3.95 (1H, d, J = 6.9), 4.04, 4.25 (2H, AB, J = 13.2), 4.17 (2H, d, J = 5.9), 4.31 (1H, dd, J = 8.2, 8.2), 6.88–6.95 (2H, m), 7.17–7.43 (7H, m)	267	–
3b	16	78	147–148	3.31–3.48 (1H, m), 3.92–4.08 (2H, overlapping), 4.13 (1H, dd, J = 6.0, 6.6), 4.20–4.31 (2H, overlapping), 4.48 (1H, dd, J = 8.7, 8.7), 4.88 (1H, d, J = 7.8), 7.08 (1H, d, J = 8.9), 7.28–7.43 (8H, m), 7.66–7.75 (2H, m)	317	–
3c	4	59	115–116	1.43–1.69 (2H, m), 1.77–1.88 (1H, m), 1.90–2.03 (2H, m), 2.15–2.26 (1H, m), 2.99 (1H, ddd, J = 4.6, 8.5, 9.0), 3.92 (1H, d, J = 12.5), 4.12–4.20 (2H, overlapping), 4.30 (1H, d, J = 9.0), 4.52 (1H, ddd, J = 4.5, 7.6, 8.5), 6.74–6.85 (3H, m), 7.10 (1H, ddd, J = 1.7, 7.6, 7.6), 7.26–7.42 (5H, overlapping)	307	–
3d	4	55	94–95	1.45–1.54 (1H, m), 1.57–1.68 (1H, m), 1.77–2.00 (3H, m), 2.13–2.23 (1H, m), 2.96 (1H, ddd, J = 4.7, 8.3, 9.0), 3.98, 4.21 (2H, AB, J = 12.2), 4.09 (1H, ddd, J = 4.7, 5.4, 5.4), 4.26 (1H, d, J = 9.0), 4.53 (1H, ddd, J = 4.3, 7.4, 8.3), 6.34 (1H, dd, J = 2.9, 8.8), 6.70–6.81 (2H, m), 7.28–7.42 (5H, m)	325	–
4a	2	84	63–64	2.62–2.70 (1H, m), 3.60 (1H, dd, J = 9.7, 9.7), 3.87–3.93 (1H, m), 4.05 (1H, dd, J = 11.6, 11.6), 4.18 (1H, dd, J = 3.8, 11.6), 4.67 (1H, br s), 5.36 (1H, d, J = 4.6), 6.94–6.99 (2H, m), 7.12 (1H, s), 7.24 (1H, d, J = 7.8), 7.33 (1H, dd, J = 7.8, 8.4), 7.37–7.43 (3H, m), 8.14–8.17 (2H, m)	283	3370
4b	1	91	143–145	2.77–2.86 (1H, m), 3.65 (1H, dd, J = 10.3, 10.3), 3.95–4.02 (1H, m), 4.05 (1H, dd, J = 12.2, 12.2), 4.26 (1H, dd, J = 3.1, 10.3), 5.09 (1H, br s), 5.86 (1H, d, J = 4.7), 7.15 (1H, d, J = 9.0), 7.19 (1H, s), 7.35–7.44 (4H, m), 7.50 (1H, ddd, J = 1.0, 7.2, 7.2), 7.78–7.86 (3H, m), 8.09–8.12 (2H, m)	333	3365
4c	2	88	283–284	0.79–0.90 (1H, m), 1.45–1.69 (3H, m), 1.96–2.38 (4H, overlapping), 4.14 (1H, br s), 4.39 (1H, br s), 5.66 (1H, d, J = 7.7), 6.82–7.01 (2H, m), 7.14–7.21 (2H, m), 7.42–7.47 (3H, m), 7.68 (1H, s), 8.28–8.31 (2H, m)	323	3340
4d	3	92	159–160	1.43–1.70 (4H, m), 1.97–2.36 (3H, overlapping), 4.15 (1H, br s), 4.37 (1H, br s), 5.61 (1H, d, J = 7.7), 6.82–6.96 (3H, m), 7.44–7.49 (3H, m), 7.69 (1H, s), 8.28–8.31 (2H, m)	341	3350
5a	6	85	66–67	2.11–2.17 (1H, m), 2.62 (3H, br s),[d] 3.85 (1H, dd, J = 5.1, 11.4), 4.03–4.11 (2H, overlapping), 4.22–4.26 (2H, overlapping), 6.81–6.93 (2H, m), 7.14–7.25 (2H, m)	179	3345, 3290
5b	12	82	111–112	2.12–2.21 (1H, m), 2.89 (3H, br s),[d] 3.91 (1H, dd, J = 5.2, 11.4), 4.15 (1H, dd, J = 3.5, 11.3), 4.33–4.37 (2H, overlapping), 4.67 (1H, d, J = 3.8), 7.04 (1H, d, J = 8.9), 7.34 (1H, dd, J = 8.0, 8.0), 7.51 (1H, dd, J = 8.0, 8.0), 7.65 (1H, d, J = 8.9), 7.77 (1H, d, J = 8.0), 7.91 (1H, d, J = 8.0)	229	3370, 3305
5c	24	88	94–95	1.52–1.66 (3H, m), 1.80 (3H, br s),[d] 1.91–2.04 (3H, m), 2.16–2.24 (1H, m), 4.30 (1H, d, J = 7.6), 4.33–4.38 (2H, overlapping), 6.77 (1H, d, J = 8.0), 6.96 (1H, dd, J = 7.4, 8.0), 7.10 (1H, dd, J = 7.4, 8.0), 7.44 (1H, d, J = 8.0)	219	3350, 3260
5d	24	78	119–120	1.51–1.70 (6H, overlapping),[e] 1.89–2.05 (3H, m), 2.13–2.23 (1H, m), 4.25 (1H, d, J = 7.5), 4.30–4.38 (2H, overlapping), 6.68–6.82 (2H, m), 7.18 (1H, dd, J = 3.0, 9.5)	237	3360, 3275

[a] Satisfactory microanalyses obtained: C ± 0.28, H ± 0.23, N ± 0.21.
[b] Yield of pure isolated product.
[c] Isoxazolidines **3** and amino alcohols **5** were recrystallized from hexane/benzene and nitrones **4** from diisopropyl ether.
[d] Exchangeable with D_2O.
[e] After deuteriation with D_2O: 3H, m.

Bruker 300 MHz apparatus. Mass spectra were taken with a VG-70EQ apparatus.

Compounds **1a**,[12] **1b**[13] and **1c**[14] were prepared according to literature.

2-(Cyclohex-2-enyloxy)-5-fluorobenzaldehyde (1d):

A suspension of 5-fluoro-2-hydroxybenzaldehyde[15] (9.1 g, 65 mmol) and K_2CO_3 (9.1 g, 65 mmol) in DMF (100 mL) was stirred for 45 min. 3-Bromocyclohexene (13.0 g, 80 mmol) was added dropwise and the mixture was stirred at r.t. for 48 h. After addition of water (100 mL), the resulting solution was extracted with Et_2O (3 × 100mL) and the organic layer was dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by distillation to give **1d**; bp 150°C/1 Torr; yield: 10.3 g (72%).

IR (Nujol): ν = 1680 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.59–1.72 (1H, m), 1.76–1.87 (1H, m), 1.90–1.97 (2H ,m), 1.99–2.18 (2H, m), 4.79–4.83 (1H, m), 5.79–5.86 (1H, m), 5.96–6.04 (1H, m), 7.01 (1H, dd, J = 4.0, 9.1 Hz), 7.17–7.25 (1H, m), 7.46 (1H, dd, J = 3.2, 8.3 Hz), 10.41 (1H, d, J = 3.2 Hz).

MS (EI): m/z = 220 (M^+).

Isoxazolidines 3a–d; General Procedure:

To a suspension of benzylhydroxylamine hydrochloride (14.7 mmol) and $NaHCO_3$ (1.49 g, 17.7 mmol) in toluene (150 mL) were added aldehyde **1** (12.3 mmol) and anhyd $CaCl_2$ (1.63 g, 14.7 mmol). The mixture was refluxed for the time given in the Table, the undissolved material was filtered and the solvent removed under reduced pressure to give **3** (Table). In the case of **3c** and **3d**, the product was

purified by chromatography on a silica gel column with light petroleum/EtOAc (3:1) as eluent.

Nitrones 4a–d; General Procedure:
A solution of **3** (10.2 mmol) in CH_2Cl_2 (50 mL) was stirred with 70% MCPBA (3.05 g, 12.3 mmol) for the time given in the Table. The mixture was washed with aq $NaHCO_3$ the organic layer was separated, dried (Na_2SO_4) and the solvent was removed under reduced pressure to give **4** (Table).

Amino Alcohols 5a–d; General Procedure:
10% Pd/C (1.4 g, 1.3 mmol) was added to a solution of **4** (8.8 mmol) in AcOH (15 mL). The mixture was stirred under H_2 for the time given in the Table and filtered through Celite. The filtrate was evaporated under reduced pressure, the residue treated with NaOH 0.5N and extracted with CH_2Cl_2. The organic phase was separated, dried (Na_2SO_4) and evaporated to give **5** (Table).

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