SHORT PAPER

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Zn–AlCl$_3$.6H$_2$O–THF system: a mild and convenient reducing agent for isoxazolidines to 1,3-amino alcohols

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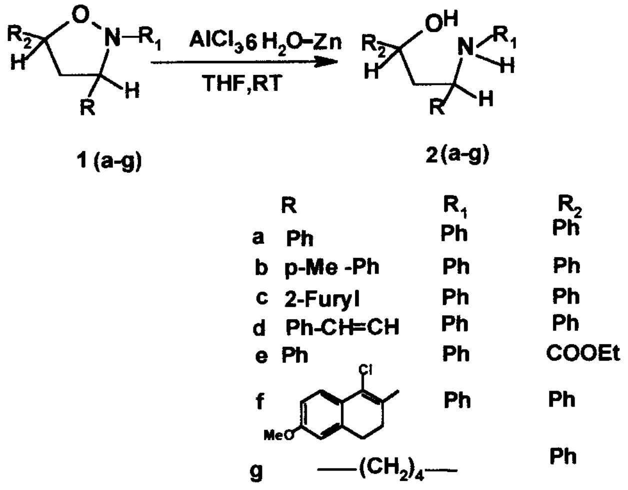
The Zn–AlCl$_3$.6 H$_2$O–THF system reduces isoxazolidines to 1,3-amino alcohols at room temperature

1,3-amino alcohols are important intermediates for biologically active and synthetically useful compounds like alkaloids,[1] carbohydrates,[2] amino acids,[3] antibiotics,[4] *etc*. Generally these compounds are prepared by reducing isoxazoline and isoxazolidine derivatives. Reducing agents for these transformations include catalytic hydrogenation over Raney nickel,[5] Pd,[6] Pt,[7] Rh,[8] aluminium amalgam[9] and lithium aluminium hydride.[10]

In recent years, reduction with bimetal systems has received renewed attention but their utility has so far been limited to organic functional group transformation[11] and C–C bond formation reactions.[12] The potential of these reagents in heterocyclic ring transformations appears to be less explored. Due to the considerable difference in redox potentials (Nerst)[13] between Al/Al^{3+} and Zn/Zn^{2+}, we assume that the combination of Zn/AlCl$_3$.6H$_2$O–THF system would be a useful reducing agent and accordingly we succeeded in selectively reducing carbon carbon double bonds,[14] nitrones to imines,[15] and the heteroaromatic oxygen–nitrogen bond of 2,1-benzisoxazoles to synthetically useful *o*-aminobenzophenones.[16] We now disclose the reductive cleavage of isoxazolidines to 1,3-amino alcohol derivatives by the reagent (Scheme 1).



Scheme 1

Regarding the mechanism of the reaction, it is likely that single electron transfer (SET) has occurred in the reduction.[12,17] Accordingly we believe that the zinc may have reduced Al^{3+} to Al(O) which is responsible for the reduction in the solvent.

In conclusion, it may be stated that a new, cheap and readily available reagent is discovered which provides a practical and simple method of preparation of 1,3-amino alcohol derivatives without side product formation in short reaction times at room temperature.

Experimental

M.p.s were determined on a Büchi apparatus. Mass spectra were recorded with a Finnigan-MAT (INCIOS -50) spectrophotometer. IR spectra were recorded on a Perkin Elmer 237 B spectrophotometer and ^{1}H NMR spectra were recorded on a Varian T-60/90 MHz spectrometer. Commercially available (BDH) AlCl$_3$.6H$_2$O and zinc dust were used directly. Tetrahydrofuran was used after distillation over KOH. Isoxazolidines were prepared as reported in the literature[9] or by modifying the reported procedure.

Typical procedure: reduction of isoxazolidines to 1,3-amino alcohol derivatives: Isoxazolidine **1a** (0.606 g, 2 mmol) was added to a vigorously stirred mixture of Zn (0.26 g, 4 mmol) and AlCl$_3$.6H$_2$O (1 g, 4 mmol) in THF (25ml) at room temperature. An exothermic reaction occurred at the beginning of the reaction, which subsided after 1.5 h. The reaction was monitored with tlc. The reaction mixture was poured into a saturated solution of NH$_4$Cl (50 ml) and extracted with diethyl ether (3 × 50 ml). The organic layer was washed with brine (2 × 50 ml) and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure gave a solid mass which was on recrystallization from pet-ether (40–60 ^{0}C) gave **2a**; Yield, 0.552g (90%); m.p. 138 ^{0}C (lit.[9] 138–9 ^{0}C); IR (KBr) ν/cm^{-1} 1500, 1600, 3000, 3250, 3600; ^{1}H NMR (CDCl$_3$) δ 2.00 and 2.70 (both dt, 2H), 3.50 (1H, OH), 4.50 (q,1H), 4.90 (q,1H), 6.50–7.40 (m, 14 H, Ar-H, 1H, NH); *m/z* 303 (M$^+$).

2b: Yield 85%; m.p. 117 ^{0}C; IR (KBr) ν/cm^{-1} 1495, 1600, 2990, 3260, 3610; ^{1}H NMR (CDCl$_3$) δ 2.30 (s,3H), and 3.10 (both dt, 2H), 3.45 (1H,OH), 4.40 (q,1H), 4.85 (q,1H), 6.40–7.75 (m, 14 H, Ar-H, 1H, NH); *m/z* 317 (M$^+$).

2c: Yield 80%; m.p. 88 ^{0}C; IR (KBr) ν/cm^{-1} 1500, 1600, 2925, 3240, 3605; ^{1}H NMR (CDCl$_3$) δ 2.30 and 3.10 (both dt, 2H), 3.45 (s,1H, OH), 4.42 (q,1H), 4.90 (q,1H), 6.00–7.20 (m, OH Ar-H, 3, Furan-H, 1H, NH); *m/z* 293 (M$^+$).

2d: Yield 95%; m.p. 108 ^{0}C; IR (KBr) ν/cm^{-1} 1500, 1600, 1650, 3000, 3250, 3615; ^{1}H NMR (CDCl$_3$) δ 1.95-2.90 (both dt, 2H), 3.45 (1H, OH), 4.10 (q, 1H), 4.70 (q ,1H), 6.10 (1H, dd), 6.50 (1H, d), 6.70–7.20 (m, 15H, Ar-H, 1H, NH); *m/z* 329(M$^+$).

2e: Yield 80%; m.p. (semi solid); IR (KBr) ν/cm^{-1} 1500, 1600, 1715, 3000, 3270, 3650; ^{1}H NMR (CDCl$_3$) δ 1.30 (t,3H), 2.15 and 3.45 (both dt, 2H), 3.55 (1H, OH), 4.13–4.40 (q, 1H), 4.50 (q, 1H), 5.44 (q, 1H), 6.55–7.50 (m, 15H, Ar-H); *m/z* 299 (M$^+$).

2f: Yield 80%; m.p. (semi solid); IR (KBr) ν/cm^{-1} 1500, 1600, 3000, 3245, 3595; ^{1}H NMR (CDCl$_3$) δ 1.95–300 (m, 6H), 2.30 (s, 3H), 3.50 (1H, OH), 4.50 (q, 1H), 4.90 (q, 1H), 6.80–7.25 (m,12H, Ar-H, 1H, NH); *m/z* 419 (M$^+$).

2g: Yield 80%; m.p. (semi solid); IR (KBr) ν/cm^{-1} 1500, 1600, 3000, 3230, 3650; ^{1}H NMR (CDCl$_3$) δ 1.30–2.30 (m ,9H, 1H, NH), 3.00-3.65 (m, 2H), 4.90 (q, 1H), 6.90-7.30 (m, 5H, Ar-H); *m/z* 205 M$^+$).

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