A Reliable Synthesis of 3-Amino-5-Alkyl and 5-Amino-3-Alkyl Isoxazoles

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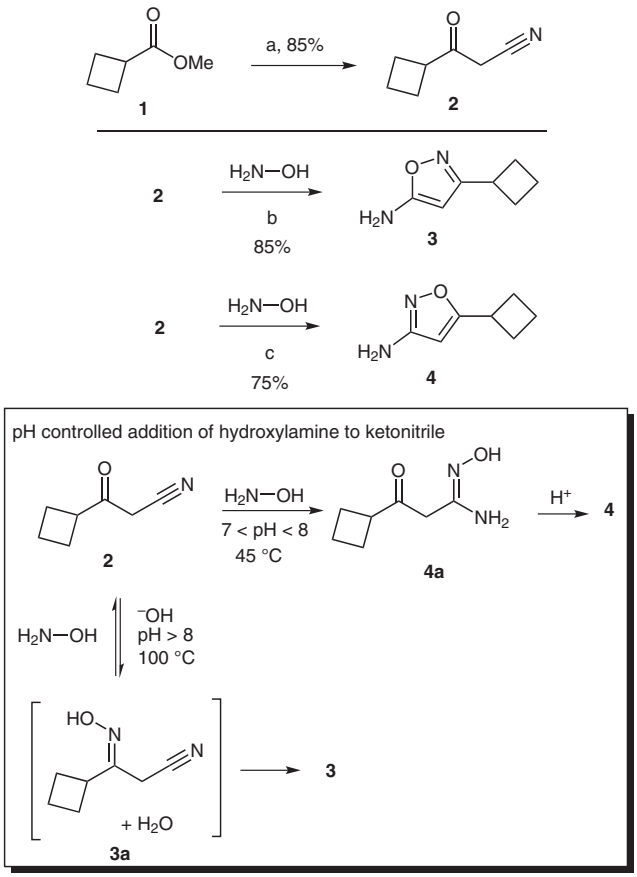
Received: 24.10.2012; Accepted after revision: 29.11.2012

Abstract: A reliable procedure that can be used to access a wide range of 3-amino-5-alkyl and 5-amino-3-alkyl isoxazoles was developed. Reaction temperature and pH were key factors that determined the regioselectivity of the two reactions.

Key words: heterocycles, regioselectivity, condensation, medicinal chemistry, imines

5-Amino- and 3-amino-isoxazoles are key building blocks in many naturally occurring molecules and pharmaceutically active synthetic compounds.[1] They have been prepared by different methods; [2] however, most of the known preparations are not very reliable, efficient, or general. A typical problem with synthesizing such amino-heterocycles is the poor yield and selectivity between formation of 3-amino and 5-amino-isoxazoles. Such amino isoxazoles became essential building blocks in our medicinal chemistry program, therefore, we decided to develop an efficient, scalable, and predictable methodology with which to access either the 3-amino or the 5-amino isomer. A typical readily accessible starting material is ketonitrile **2**, which can be obtained from condensation of commercially available cyclobutyl-acetic acid methyl ester **1** and lithiated acetonitrile (Scheme 1)[3] or is available from commercial sources.[4] We explored several reaction conditions involving **2** and hydroxylamine and found that formation of 5-amino isoxazoles was the preferred pathway regardless of the number of equivalents of hydroxylamine, the base, or the temperature used. Upon careful monitoring of the reaction,[2f] we discovered that it was governed by the pH obtained following mixing the hydroxylamine salts, the chosen base, and the temperature. In fact, these parameters were responsible for directing the addition of the hydroxylamine either towards the ketone (pH > 8, giving 5-amino-isoxazole; **3a**, Scheme 1) or the nitrile (7 < pH < 8, giving 3-amino-isoxazole; **4a**, Scheme 1), hence, generating the two possible isomers upon acid-mediated cyclization.[2f] Towards the synthesis of the 3-amino isomer, we also found that keeping the temperature at or below 45 °C (Scheme 1, d), was critical to allow keto-nitriles bearing a less bulky group to still undergo addition of hydroxylamine to the nitrile, leading to the desired isomer.[5] 1D and 2D NMR studies of derivatives of each isoxazole isomer (see the Supporting Information) allowed their regiochemistry to be unequivocally assigned.

Selected examples (Table 1) highlight the generality of these methods to access 3- or 5-alkyl amino isoxazoles. It is worth noting that even enolizable ketones (entries 1–3 and 6), especially those that are less hindered (entry 6), provide good yields of both 5-amino and 3-amino isoxazoles. Electron-withdrawing groups (entry 5) do not seem to have an effect on either the condensation or cyclization reactions.

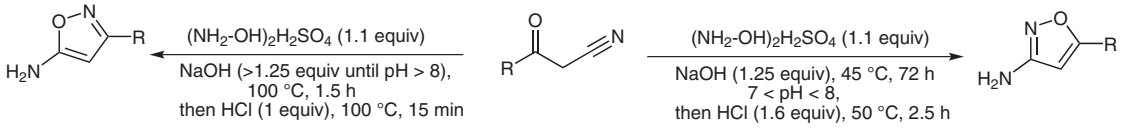


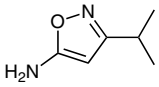
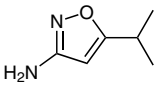
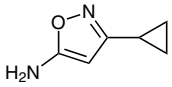
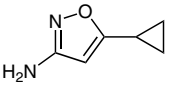
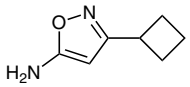
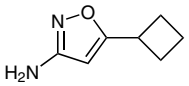
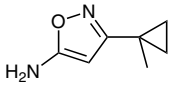
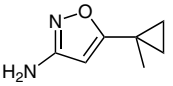
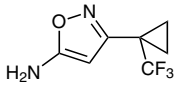
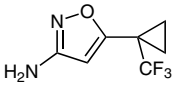
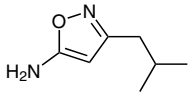
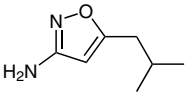
Scheme 1 Exploring regioselectivity. *Reagents and conditions*: (a) LDA, MeCN, THF, –78 °C to r.t., 2 h; (b) NaOH (pH > 8), H_2O, 100 °C, 1.5 h then HCl, 100 °C, 15 min; (c) NaOH (7 < pH < 8), H_2O, 45 °C, 72 h, then HCl, 50 °C, 2.5 h.

In conclusion, a general and reliable method that can be used to access both 3-amino-5-alkyl and 5-amino-3-alkyl-isoxazole isomers is reported. It is anticipated that this method will allow greater access to more complex varia-

SYNTHESIS 2013, 45, 0171–0173
Advanced online publication: 19.12.2012
DOI: 10.1055/s-0032-1317935; Art ID: SS-2012-M0836-OP

Table 1 Substrate Scope for the Selective Formation of 3-Amino and 5-Amino Isoxazoles



Entry	5-Amino yield (%)	R	3-Amino yield (%)
1	 **5** (70)	 **15**	 **6** (60)
2	 **7** (70)	 **16**	 **8** (65)
3	 **3** (85)	 **2**	 **4** (75)
4	 **9** (85)	 **17**	 **10** (60)
5[a]	 **11** (71)	 **18**	 **12** (70)
6	 **13** (90)	 **19**	 **14** (60)

[a] Reaction leading to **12** contained 50% **11**.

tions of this pharmaceutically relevant heterocycle and may eventually lead to their commercial availability.

All reagents and solvents were used as supplied. All reactions were performed under a nitrogen atmosphere unless otherwise stated. ^{1}H NMR spectra were recorded by using an internal deuterium lock at ambient temperature with a Bruker 400 Ultrashield spectrometer. Data are presented as follows: chemical shift (in ppm on the δ scale relatively to δ = 0 ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet, m = multiplet, br = broad, dd = doublet of doublet, dt = doublet of triplet, dq = doublet of quartet), coupling constant (*J* in Hz) and integration. Mass spectra were recorded with an Agilent 1200 liquid chromatograph. The resolution of the MS system was approximately 11000 (FWHM definition). Keto-nitriles **2**, **15**–**17**, and **19** are available from commercial sources.[4]

3-Oxo-3-[1-(trifluoromethyl)cyclopropyl]propanenitrile (18)

To a solution of diisopropylamine (1.934 mL, 13.68 mmol) in THF (59.5 mL) at –78 °C, butyllithium (2.7 M in heptane, 5.07 mL, 13.68 mmol) was added. The solution was warmed to r.t. and stirred for 30 min, then cooled to –78 °C again and a solution of methyl 1-(trifluoromethyl)cyclopropanecarboxylate (1.0 g, 5.95 mmol) in MeCN (0.63 mL, 11.90 mmol) was added dropwise. The reaction was stirred at –78 °C for 10 min then warmed to r.t. for 2 h. The reaction was quenched with 1 M HCl (20 mL), washed again with 1 M HCl (20 mL), extracted with EtOAc (2 × 50 mL), dried with $MgSO_4$, filtered, and concentrated to give the title compound.

Yield: 1.05 g (99%); colorless oil.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.14 (s, 2 H), 1.65–1.75 (m, 2 H), 1.46–1.55 (m, 2 H).

MS (ESI): *m*/*z* = 173.9 [M + 1].

5-Isopropylisoxazol-3-ylamine (6); Typical Procedure

To a mixture of 4-methyl-3-oxopentanenitrile **15** (11 g, 99 mmol) and H_2O (200 mL) was added NaOH (4.95 g, 124 mmol). When the NaOH pellets had completely dissolved, hydroxylamine sulfate (8.93 g, 109 mmol) was added and, after 5 min, the pH was measured (pH 7–8). The reaction is warmed to 45 °C and stirred for 72 h. HCl (13.0 mL, 158 mmol, 37%) was added in one portion and the reaction was warmed to 50 °C for 2.5 h. The reaction was removed from the oil bath and allowed to cool to r.t., then a solution of NaOH (30% in H_2O) was added to adjust the solution to pH 11. EtOAc was then added and the layers separated. The aqueous layer was extracted with EtOAc (3 × 200 mL) until no more product was found in the

water layer as measured by LCMS. The combined organics were dried (Na_2SO_4) and evaporated to give the title compound.

Yield: 7.5 g (60%); yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.52 (s, 1 H), 5.4 (s, 2 H), 2.84–2.87 (m, 1 H), 1.11–1.24 (m, 6 H).

MS (ESI): *m*/*z* = 127.2 [M + 1].

5-Cyclopropylisoxazol-3-ylamine (8)
Yield: 4.0 g (65%); pale-yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.50 (s, 1 H), 5.37 (s, 2 H), 1.88–1.98 (m, 1 H), 0.87–0.96 (m, 2 H), 0.70–0.77 (m, 2 H).

MS (ESI): *m*/*z* = 125.2 [M + 1].

5-Cyclobutylisoxazol-3-ylamine (4)
Yield: 2.2 g (75%); pale-yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.6 (s, 1 H), 5.4 (s, 2 H), 3.4–3.5 (m, 1 H), 1.7–2.2 (m, 6 H).

MS (ESI): *m*/*z* = 139.2 [M + 1].

5-(1-Methylcyclopropyl)isoxazol-3-ylamine (10)
Yield: 1.2 g (60%); pale-yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.52 (s, 1 H), 5.38 (s, 2 H), 1.3 (s, 3 H), 0.81–0.95 (m, 2 H), 0.72–0.8 (m, 2 H).

MS (ESI): *m*/*z* = 139.2 [M + 1].

5-[1-(Trifluoromethyl)cyclopropyl]isoxazol-3-amine (12)
Yield: 0.2 g (70%); pale-yellow solid; contained 50% **11**. Data for compound **12**.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.63 (s, 1 H), 5.43 (s, 2 H), 1.38–1.45 (m, 4 H).

MS (ESI): *m*/*z* = 193.2 [M + 1].

5-Isobutylisoxazol-3-ylamine (14)
Yield: 0.6 g (60%); pale-yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.91 (s, 1 H), 4.83 (s, 2 H), 2.31 (d, *J* = 7.07 Hz, 2 H), 1.86–1.93 (m, 1 H), 0.93–0.96 (m, 6 H).

MS (ESI): *m*/*z* = 141.5 [M – 1].

3-Isopropylisoxazol-5-ylamine (5); Typical Procedure
A solution of hydroxylamine sulfate (1.72 g, 20.9 mmol) in H_2O (4 mL) was added to a solution of 5-methyl-3-oxo-hexanenitrile (2.38 g, 19.0 mmol) and NaOH (0.837 g, 20.9 mmol) in H_2O (10 mL) at r.t. The mixture was adjusted to pH > 8 (between pH 8 and 11) with 5% NaOH, then heated to 100 °C for 1.5 h. Concentrated HCl (1.73 mL, 17.1 mmol) was added and the mixture was heated at 100 °C for 15 min. After cooling, the pH was adjusted to 11 with 30% NaOH and the mixture was extracted with EtOAc (3 × 20 mL). The organic extracts were dried with Na_2SO_4 and concentrated to give the title compound.

Yield: 1.7 g (70%); yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.44 (s, 2 H), 4.81 (s, 1 H), 2.73 (quint, *J* = 6.88 Hz, 1 H), 1.02–1.23 (m, 6 H).

MS (ESI): *m*/*z* = 127.2 [M + 1].

3-Cyclopropylisoxazol-5-ylamine (7)
Yield: 0.6 g (70%); white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.43 (s, 2 H), 4.61 (s, 1 H), 1.73 (tt, *J* = 8.43, 4.96 Hz, 1 H), 0.80–0.95 (m, 2 H), 0.52–0.68 (m, 2 H).

MS (ESI): *m*/*z* = 123.2 [M – 1].

3-Cyclobutylisoxazol-5-ylamine (3)
Yield: 1.1 g (85%); pale-yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.47 (s, 2 H), 4.86 (s, 1 H), 3.22–3.39 (m, 1 H), 1.74–2.28 (m, 6 H).

MS (ESI): *m*/*z* = 139.2 [M + 1].

3-(1-Methylcyclopropyl)isoxazol-5-ylamine (9)
Yield: 0.6 g (85%); white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.41 (br. s., 2 H), 4.64 (s, 1 H), 1.28 (s, 3 H), 0.76–0.97 (m, 2 H), 0.63–0.76 (m, 2 H).

MS (ESI): *m*/*z* = 139.2 [M + 1].

3-(1-Methylcyclopropyl)isoxazol-5-ylamine (11)
Yield: 1.4 g (71%); pale-yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.71 (br. s., 2 H), 4.9 (s, 1 H), 1.21–1.37 (m, 4 H).

MS (ESI): *m*/*z* = 193.2 [M + 1].

3-(1-Methylcyclopropyl)isoxazol-5-ylamine (13)
Yield: 0.5 g (90%); pale-yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.44 (s, 2 H), 4.78 (s, 1 H), 2.23 (d, *J* = 7.07 Hz, 2 H), 1.84 (dt, *J* = 13.64, 6.82 Hz, 1 H), 0.88 (d, *J* = 6.57 Hz, 6 H).

MS (ESI): *m*/*z* = 141.5 [M – 1].

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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(5) Takase and co-workers in ref. 2f report the formation, with reasonable yields, of only 5-aminoisoxazole for any group smaller than *t*-Bu at 100 °C.