Carbamate Oxime Reduction: A New Route to C3-Amino-1,4-benzodiazepines

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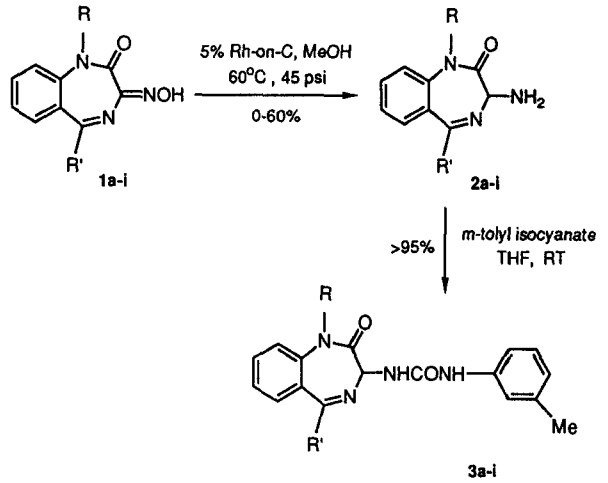
A mild reduction method of C3-oximido-1,4-benzodiazepines to afford the C3-amino derivatives is described. The key step involves the formation of a carbamate oxime intermediate. The greater reactivity of the C3-(ethylaminocarbonyl)oximido-1,4-benzodiazepine towards hydrogenation, compared to the parent C3-oxime, enables the reduction to take place at ambient temperature using palladium-on-carbon. The mild conditions are more suitable for sensitive amines such as 3,5-diamino-1,4-benzodiazepines.

C3-Amino-1,4-benzodiazepine derivatives are an important class of biologically active substances, for example in benzodiazepine substituted peptides, which are effective farnesyltransferase inhibitors,[1] and C3-amido and C3-ureido-1,4-benzodiazepines, which are high affinity ligands for the cholecystokinin type A (CCK_A) and type B (CCK_B) receptors, respectively.[2-4] Over the years, efforts have been made to improve the synthesis of C3-aminobenzodiazepines of the type **2**. Early methods involved synthesis of the benzodiazepine nucleus with the amine functionality already in place,[5] which necessitated lengthy reaction sequences, and **2** was only obtained in low yield. Subsequently, more efficient methods were developed and optimised to suit the C5-phenylbenzodiazepine series.[6]

Recently, a novel series of amidine benzodiazepines (**3**, R′ = amine) were prepared in our laboratories.[7] Using previously described methodology,[8] attempts to build the benzodiazepine core in this series using isopropylthio-N^{α}-benzyloxycarbonylglycine and methyl *N*-methylanthranilate failed to provide the required advanced C3-amino intermediates[9] (**2**, R′ = amine) necessary for the urea formation. An alternative synthetic route toward the amidines involved the preparation of the benzodiazepine ring system and subsequent introduction of the C3-amino group at a later stage. Following the precedent in the C5-phenyl series,[6] introduction of the C3-amine via catalytic reduction of the corresponding oxime (**1**, R′ = amine) was attempted. The relatively harsh conditions (elevated temperature) used in the oxime reduction step proved to be largely incompatible with the presence of the amidine group, yields of the amine being lower than in the case of the C5-phenylbenzodiazepines. Under these conditions, the amidine amines (**2**, R′ = amine) proved to be unstable in solution over extended periods of time. The present study describes a more efficient method, which includes derivatisation of the oxime and subsequent reduction, to obtain the C3-aminobenzodiazepine in the amidine series. This new route is also suitable for the C5-phenyl- and C5-cyclohexylbenzodiazepine series. The new procedure is compared with direct reduction of the oxime.

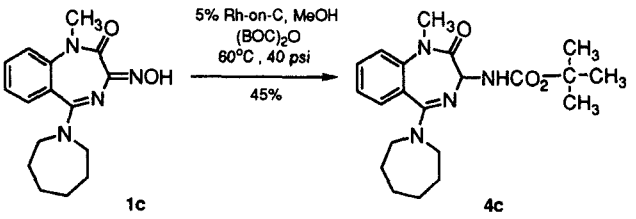
In the C5-phenyl series, direct reduction of the oxime was achieved by hydrogenation at 70 °C under 40 psi of hydrogen, using 5 % ruthenium-on-carbon as catalyst for 24 hours.[6] This method, which gave good yields (80 %) in this series, was not suitable for the amidine analogues.

The use of rhodium-on-carbon as an alternative catalyst reduced the reaction time but did not significantly improve the yields (Scheme 1) (Table 1).



Scheme 1

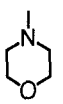
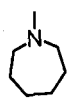
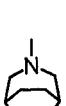
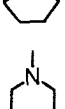
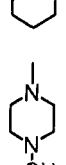
Other routes were also explored: chemical methods such as zinc–trifluoroacetic acid in acetic acid[10] led to total decomposition of **2a–f** (compounds **2g–i** were reduced but in very low yield) and transfer hydrogenation[11] in the presence of cyclohexene and rhodium-on-carbon did not give any reduction. Attempts to stabilise the amine in solution during the hydrogenation step were not particularly successful. For example addition of one equivalent of acid did, in fact, increase the decomposition rate of **2**, but incorporation of di-*tert*-butyl carbonate to protect the amine in situ was more satisfactory (Scheme 2), leading to a twofold improvement in the yield of the reduction step.



Scheme 2

In order to facilitate oxime reduction in the amidine series, *O*-acyl oximes were investigated. It was felt that the electron-withdrawing capability of the carbamate group might confer greater reactivity toward hydrogenation of the C=N and N–O bonds compared to those in the oxime **1**. The ethyl carbamate derivative was chosen because of the volatility, and hence ease of removal, of

Table 1. Compounds **3a–i** Prepared

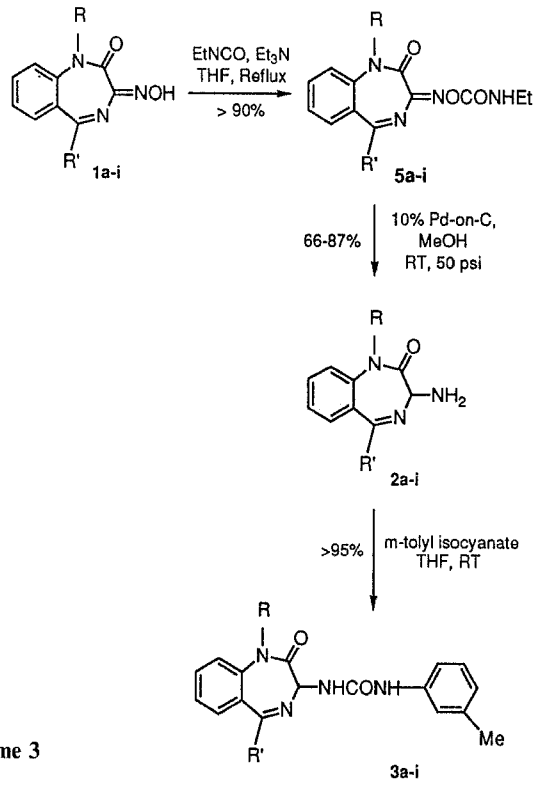
Compound	R	R'	Yield[a] (%)	Yield[b] (%)	mp (°C)	MS[c] *m/z*	^{1}H NMR[d] δ, *J* (Hz)
3a	Me		14 (13)	75	245–249	392	1.70–1.83 (m, 2H, CH_2), 1.83–1.95 (m, 2H, CH_2), 2.21 (s, 3H, CH_3), 3.00–3.12 (m, 2H, 2 × CH), 3.30 (s, 3H, CH_3), 3.38–3.50 (m, 2H, 2 × CH), 4.96 (d, *J* = 8, 1H, CH), 6.92 (d, *J* = 8, 1H, NH), 6.68–7.66 (m, 8H, arom), 8.77 (br s, 1H, NH)
3b	Me		18 (5)	82	259–261	408	2.21 (s, 3H, CH_3), 3.08–3.15 (m, 4H, 2 × CH_2), 3.35 (s, 3H, CH_3), 3.54–3.75 (m, 4H, 2 × CH_2), 4.94 (d, *J* = 8, 1H, CH), 7.04 (d, *J* = 8, 1H, NH), 6.70–7.70 (m, 8H, arom), 8.82 (br s, 1H, NH)
3c	Me		25	80	210–211	420	1.44–1.84 (m, 8H, 4 × CH_2), 2.28 (s, 3H, CH_3), 3.34–3.50 (m, 4H, 2 × CH_2), 3.41 (s, 3H, CH_3), 5.23 (d, *J* = 8, 1H, CH), 6.35 (d, *J* = 8, 1H, NH), 6.80–7.50 (m, 9H, arom + NH)[e]
3d	*i*-Bu		8	78	178–180	462	0.68 (d, *J* = 7, 3H, CH_3), 0.78 (d, *J* = 7, 3H, CH_3), 1.40–1.80 (m, 9H, 4 × CH_2 + CH), 2.21 (s, 3H, CH_3), 3.30 (s, 3H, CH_3), 3.36–3.38 (m, 2H, 2 × CH), 3.53 (dd, *J* = 5; 14, 1H, CH), 4.11 (dd, *J* = 9; 14, 1H, CH), 4.86 (d, *J* = 8, 1H, CH), 6.90 (d, *J* = 8, 1H, NH), 6.70–7.68 (m, 8H, arom), 8.78 (br s, 1H, NH)
3e	Me		20	80	> 242 dec.	446	1.54–2.04 (m, 10H, 4 × CH_2 + 2 × CH), 2.29 (s, 3H, CH_3), 3.26–3.40 (m, 2H, 2 × CH), 3.42 (s, 3H, CH_3), 3.52–3.60 (m, 2H, 2 × CH), 5.28 (d, *J* = 8, 1H, CH), 6.44 (d, *J* = 8, 1H, NH), 6.80–7.55 (m, 9H, arom + NH)[e]
3f	Pr		10	85	232–234	434	0.70 (t, *J* = 7, 3H, CH_3), 1.20–1.66 (m, 8H, 4 × CH_2), 2.21 (s, 3H, CH_3), 3.08–3.20 (m, 4H, 2 × CH_2), 3.60–3.69 (m, 1H, CH), 4.17–4.27 (m, 1H, CH), 4.92 (d, *J* = 8, 1H, CH), 6.99 (d, *J* = 8, 1H, NH), 6.71–7.65 (m, 8H, arom), 8.81 (br s, 1H, NH)
3g	Me		26 (19)	87	230–234	421	2.19 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 2.24–2.34 (m, 2H, 2 × CH), 2.40–2.50 (m, 2H, 2 × CH), 3.06–3.20 (m, 4H, 2 × CH_2), 3.33 (s, 3H, CH_3), 4.95 (d, *J* = 8, 1H, CH), 7.03 (d, *J* = 8, 1H, NH), 6.70–7.70 (m, 8H, arom), 8.81 (br s, 1H, NH)
3h	Me		60 (80)[f]	68	> 210 dec.	399	2.24 (s, 3H, CH_3), 3.41 (s, 3H, CH_3), 5.24 (d, *J* = 8, 1H, CH), 6.71–7.77 (m, 14H, arom + NH), 8.97 (s, 1H, NH)
3i	Me		0[g]	66	210–212	405	0.85–1.96 (m, 10H, 5 × CH_2), 2.22 (s, 3H, CH_3), 2.86–2.98 (m, 1H, CH), 3.32 (s, 3H, CH_3), 5.06 (d, *J* = 8, 1H, CH), 6.70–7.80 (m, 9H, arom + NH), 8.88 (s, 1H, NH)

[a] Yield (%) of isolated urea obtained via the direct reduction of the oxime using 5% Rh-on-C. Ruthenium-on-carbon yields are indicated in parentheses where appropriate.
[b] Yield of isolated urea obtained via the reduction of the carbamate oxime using 10% Pd-on-C.
[c] MS (Cl^+): *m/z* for $(M + H)^+$.
[d] NMR run in DMSO-d_6 unless stated.
[e] NMR run in $CDCl_3$.
[f] See ref. 6.
[g] A 15% yield has been reported using Zn, TFA, AcOH, see ref. 13.

excess ethyl isocyanate and the subsequent byproducts of the reduction, ethyl amine and carbon dioxide. Lower yields obtained for the C5-phenyl and C5-cycloalkyl series (Table 1) suggest that in addition to the electron-withdrawing nature of the carbamate, the electron-donating capability of the amidine moiety may be important in increasing the reactivity of the C=N bond towards reduction.

One equivalent of benzodiazepine oximes **1a–i** was stirred, under reflux, with three equivalents of ethyl isocyanate and one equivalent of triethylamine in tetrahydrofuran (Scheme 3). The presence of triethylamine significantly reduced the reaction time. The activated carbamate oximes **5a–i** were obtained in quantitative yield (Table 2). Oximes **5a–i** were then readily reduced to the amines **2a–i** at ambient temperature under a hydrogen pressure of 50 psi, using 10% palladium-on-carbon as catalyst. The benzodiazepine amines **2a–i** were obtained in very high purity, and were reacted immediately with *m*-tolyl isocyanate in tetrahydrofuran to provide the final benzodiazepine ureas in excellent yield (Table 1).

Direct reduction of the benzodiazepine oximes was performed at 60 °C under 45 psi of hydrogen, using a weight equivalent quantity of catalyst (5% rhodium or 5% ruthenium-on-carbon) (Scheme 1). In the case of the amidine the majority of the formed amine decomposed while the reaction proceeded. The crude reaction mixture was then treated with *m*-tolyl isocyanate as above. It was observed that, during the direct reduction of the oxime with rhodium-on-carbon, the larger the N1 substituent (Me to *i*-Bu), the poorer the hydrogenation yield obtained. This was not the case when the carbamate reduction methodology was employed.



Scheme 3

The present study describes a new method to obtain C3-amino benzodiazepines, using ethyl carbamate oxime derivatives as intermediates. This route is compatible with the presence of the amidine functionality and is also well tolerated by other 1,4-benzodiazepine systems.

All melting points were taken in open capillaries and are uncorrected. ^{1}H NMR spectra were measured on a Bruker AM 360 (360 MHz) spectrometer with TMS as internal standard. Mass spectra were obtained using a VG Quattro (55 eV) spectrometer. Microanalysis were carried out in the Analytical Department of Butterworth Laboratories, Teddington, Middlessex. Compounds **3a–i, 4c** and **5a–i** gave C,H,N ± 0.37 except **3e**, H −0.4 and **5a,c,g**, N ± 0.48 %. All benzodiazepine oximes were obtained using methods previously described.[6,12,13] Other reagents were commercially available.

3-Ethylaminocarbonyloxyimino-1,4-benzodiazepin-2-ones 5a–i; General Procedure:

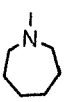
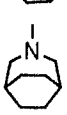
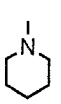
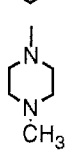
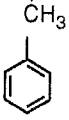
3-Hydroxyimino-1,4-benzodiazepin-2-ones **1a–i** (500 mg, 1.8 mmol), ethyl isocyanate (0.44 mL, 5.5 mmol) and Et_3N (0.26 mL, 1.8 mmol) were heated to reflux (Table 2) in THF (50 mL). The solvent was evaporated and the residue was purified by column chromatography on silica ($MeOH/CH_2Cl_2$, gradient).

3-Amino-1,4-benzodiazepin-2-ones 2a–i; General Procedure:

Method A; From oxime ethers **5a–i**:

Oxime ethers **5a–i** (300 mg) were hydrogenated at 50 psi in MeOH

Table 2. Compounds **5a–i** Prepared

Compound	R	R'	Yield[a] (time/h)	mp (°C)	MS[b] *m/z*	^{1}H NMR[c] *δ*, *J* (Hz)
5a	Me		97 (0.75)	> 110 sintered	344	1.12 (t, *J* = 7, 3H, CH_3), 1.78–2.14 (m, 4H, 2 × CH_2), 3.25 (q, *J* = 7, 2H, CH_2), 3.16–3.30 (m, 1H, CH), 3.44 (s, 3H, CH_3), 3.56–3.68 (m, 2H, 2 × CH), 3.76–3.88 (m, 1H, CH), 6.35–6.44 (m, 1H, NH), 7.30–7.52 (m, 4H, arom)
5b	Me		92 (4)	> 110 sintered	360	1.15 and 1.17 (t, *J* = 7, 3H, CH_3), 3.20–3.30 (m, 2H, CH_2), 3.45 and 3.47 (s, 3H, CH_3), 3.53–3.88 (m, 8H, 4 × CH_2), 6.00–6.06 and 6.32–6.40 (m, 1H, NH), 7.20–7.58 (m, 4H, arom)
5c	Me		95 (4)	> 100 sintered	372	1.12 (t, *J* = 7, 3H, CH_3), 1.35–1.98 (m, 8H, 4 × CH_2), 3.20–3.30 (m, 2H, CH_2), 3.44 (s, 3H, CH_3), 3.42–3.58 (m, 3H, CH + CH_2), 4.00–4.08 (m, 1H, CH), 6.35–6.44 (m, 1H, NH), 7.19–7.52 (m, 4H, arom)
5d	*i*-Bu		98 (6)	> 90 sintered	414	1.22 (t, *J* = 7, 3H, CH_3), 1.34–1.96 (m, 8H, 4 × CH_2), 3.20–3.31 (m, 2H, CH_2), 3.44 (s, 3H, CH_3), 3.42–3.58 (m, 3H, CH + CH_2), 4.01–4.11 (m, 1H, CH), 6.36–6.44 (m, 1H, NH), 7.20–7.50 (m, 4H, arom)
5e	Me		95 (3)	> 168 sintered	398	1.10 and 1.12 (t, *J* = 7, 3H, CH_3), 1.24–1.96 (m, 9H, 4 × CH_2 + CH), 2.16–2.28 (m, 1H, CH), 3.12–3.52 (m, 4H, 2 × CH + CH_2), 3.44 and 3.45 (s, 3H, CH_3), 3.58–3.70 (m, 1H, CH), 4.56–4.78 (m, 1H, CH), 6.13–6.22 and 6.36–6.44 (m, 1H, NH), 7.18–7.52 (m, 4H, arom)
5f	Pr		94 (1.25)	> 90 sintered	386	0.85 (t, *J* = 7, 3H, CH_3), 1.12 (t, *J* = 7, 3H, CH_3), 1.40–1.80 (m, 8H, 4 × CH_2), 3.20–3.30 (m, 2H, CH_2), 3.36–3.92 (m, 4H, 2 × CH_2), 3.50–3.62 (m, 1H, CH), 4.46 (dd, *J* = 7.5; 14, 1H, CH), 6.35–6.44 (m, 1H, NH), 7.20–7.51 (m, 4H, arom)
5g	Me		97 (5)	> 80 sintered	373	1.11 and 1.13 (t, *J* = 7, 3H, CH_3), 2.37 and 2.39 (s, 3H, CH_3), 2.40–2.70 (m, 4H, 2 × CH_2), 3.20–3.30 (m, 2H, CH_2), 3.45 and 3.47 (s, 3H, CH_3), 3.50–4.06 (m, 4H, 2 × CH_2), 6.01–6.09 and 6.33–6.42 (m, 1H, NH), 7.22–7.58 (m, 4H, arom)
5h	Me		97 (4)	> 105 sintered	368[d]	1.15 and 1.16 (t, *J* = 7, 3H, CH_3), 3.24–3.35 (m, 2H, CH_2), 3.33 (s, 3H, CH_3), 5.96–6.02 and 6.28–6.38 (m, 1H, NH), 7.22–7.88 (m, 9H, arom)
5i	Me		98 (7)	> 85 sintered	373[d]	1.13 (t, *J* = 7, 3H, CH_3), 1.18–1.42 (m, 4H, 2 × CH + CH_2), 1.52–1.78 (m, 4H, 4 × CH), 1.86–1.97 (m, 1H, CH), 2.16–2.26 (m, 1H, CH), 2.87–2.99 (m, 1H, CH), 3.20–3.34 (m, 2H, CH_2), 3.44 (s, 3H, CH_3), 6.20–6.28 (m, 1H, NH), 7.24–7.60 (m, 4H, arom)

[a] Yield (%) of isolated carbamate oxime after column chromatography.
[b] MS (Cl^+): *m/z* for $(M + H)^+$.
[c] ^{1}H NMR were run in $CDCl_3$.
[d] MS (Cl^+): *m/z* for $(M + NH_4)^+$.

(compounds **a** to **g**) or EtOAc (compounds **h** and **i**) (30 mL) over 10% palladium-on-carbon (100 mg) for 3 h at r.t. The mixture was filtered, then evaporated to dryness to afford the amine as a foam, which was used immediately in the next step.

Method B1; From 3-hydroxyimino-1,4-benzodiazepin-2-ones **1a–i**:

Oximes **1a–i** (300 mg) were hydrogenated at 45 psi in MeOH (30 mL) over 5% rhodium-on-carbon (300 mg) for 7 h at 60 °C. The mixture was filtered, then evaporated to dryness to afford the amine as an oil, which was used immediately in the next step.

Method B2; From 3-hydroxyimino-1,4-benzodiazepin-2-ones **1a,b,g**:

Oximes **1a, b, g** (300 mg) were hydrogenated at 45 psi in MeOH (30 mL) over 5% ruthenium-on-carbon (300 mg) for 24 h at 60 °C. The mixture was filtered, then evaporated to dryness to afford the amine as an oil which was used immediately in the next step. The reaction conditions were not optimised.

N-(2-Oxo-1,4-benzodiazepin-3-yl)-N'-(3-methylphenyl)ureas 3a–i; General Procedure:

To a solution of the crude amines **2a–i** (0.87 mmol) in THF (3 mL) was added *m*-tolyl isocyanate (0.11 mL, 0.87 mmol). The solution was stirred for 5 min at r.t. and left to stand at 4 °C overnight. The precipitate was collected and the mother liquor purified by column chromatography on silica gel ($MeOH/CH_2Cl_2$, gradient) to afford further product.

3-(*R,S*)-3-(*tert*-Butyloxycarbonylamino)-1-methyl-5-(perhydroazepin-1-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (4c):

3-Hydroxyimino-1-methyl-5-(perhydroazepin-1-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one **(1c)** (115 mg, 0.38 mmol) was hydrogenated at 40 psi in MeOH (20 mL) over 5% rhodium-on-carbon for 7.5 h at 60 °C in the presence of di-*tert*-butyl carbonate (165 mg, 0.77 mmol). The mixture was filtered, then evaporated to dryness to afford the protected amine as an oil. The oil was purified by column chromatography on silica ($MeOH/CH_2Cl_2$, gradient) to give the title compound **4c** (66 mg, 45%), mp 160–165 °C.

^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.30–1.90 (m, 8H, $4 \times CH_2$), 1.41 (s, 3H, CH_3), 3.30–3.50 (m, 4H, $2 \times CH_2$), 3.39 (s, 3H, CH_3), 5.01 (d, J = 8, 1H, CH), 6.03 (d, J = 8, 1H, NH), 7.16–7.50 (m, 4H, arom).

MS (Cl^+): m/z = 387 for $(M + H)^+$.

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