Synthesis of ene-1,1-diamines and pyrrolo[1,2-*a*]imidazolediones by 4,5-dihydroimidazole *N*-oxide cycloaddition and isoxazoline ring opening

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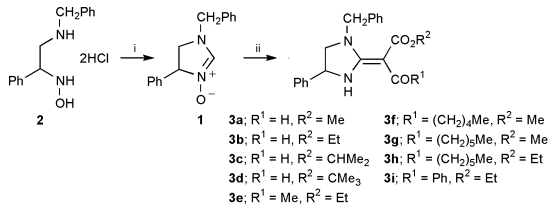
Dihydroimidazole *N*-oxides 1 undergo 1,3-dipolar cycloaddition with alkyne dipolarophiles and the cycloadducts suffer isoxazoline N–O bond cleavage to afford ene-1,1-diamines, with subsequent cyclisation to pyrrolo[1,2-*a*]imidazole-5,6-diones if possible.

We have recently described the synthesis of 4,5-dihydroimidazolium 3-oxide **1**, and its diastereoselective 1,3-dipolar cycloaddition reactions with alkenes to produce the rarely reported imidazo[1,2-*b*]isoxazoles (Scheme 1).[1] These latter, on N–O reduction and recyclisation, are potential sources for chiral pyrroloimidazoles and thence for pyrrolidines. Whilst exploring the reactions of this dipole with alkynes we isolated unexpected ene-1,1-diamine products which correspond to a C–C bond formation at C-2 of the dihydroimidazole ring with transfer of the nitrone oxygen atom to the new side-chain. Where possible, a second cyclisation to give pyrroloimidazole-5,6-diones is observed. We report these results herein and account for them in terms of the predicted 1,3-dipolar cycloadditions followed by isoxazoline ring opening. Ene-1,1-diamines are useful reagents in heterocyclic synthesis and in some cases possess biological activities.[2] Our results represent a new approach to such systems, that is very different from 'traditional' enediamine synthesis, *e.g.* from diamines with ketene acetals, or cyclic ureas with active methylene compounds,[2] or from acylation of 2-methyl cyclic amidines.[3] Biological activity has also been recorded for some pyrrolo[1,2-*a*]imidazoles.[4]

The nitrone **1** as its hydrochloride salt was prepared *in situ* from the aminohydroxylamine **2** dihydrochloride as previously described,[1] by treatment with triethyl orthoformate (toluene, 60 °C), and used directly. Reaction of the nitrone hydrochloride solution with methyl propynoate (1.25 eq., Et_3N, 2.1 eq., 60 °C, 18 h) led to isolation of the formyl alkoxycarbonyl enediamine **3a** (Scheme 2, Table 1). Similar reactions were observed with ethyl, 2-propyl and *tert*-butyl propynoates to afford further enediamines **3b**–**d** (Scheme 2, Table 1). With other 2-alkynoates (namely ethyl but-2-ynoate, methyl oct-2-ynoate, methyl and ethyl non-2-ynoate, and ethyl 3-phenylpropynoate) as reaction partner for the nitrone **1**, the corresponding alkanoyl alkoxycarbonyl enediamines **3e**–**i** were observed as the products.[5,6]

The products **3** are represented as the enaminoketone tautomer A (Fig. 1), although they may in principle also exist as the imino–enol tautomer B. Solution spectroscopy suggests the enaminoketone representation. All of **3a**–**i** display a peak in the



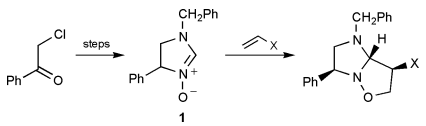
Scheme 2 *Reagents*: i, $(EtO)_3CH$, toluene, 60 °C; $R^1C{\equiv}CCO_2R^2$, Et_3N, 60 °C.

Table 1 1,1-Enendiamines **3** from reaction of imidazoline 1-oxide **1** and 2-alkynoates (Scheme 2)

R^1	R^2	1,1-Enendiamines **3** (yield %)
H	Me	**3a** (37)
H	Et	**3b** (18)
H	$CHMe_2$	**3c** (55)
H	CMe_3	**3d** (45)
Me	Et	**3e** (58)
$(CH_2)_4Me$	Me	**3f** (80)
$(CH_2)_5Me$	Me	**3g** (56)
$(CH_2)_5Me$	Et	**3h** (48)
Ph	Et	**3i** (51)

^{13}C NMR spectrum for a conjugated aldehyde (δ 186–187 for **3a**–**d**) or ketone (δ 193–197 for **3e**–**i**), respectively. The resonances for the enamine double bond are observed in the ranges δ 85–90 (NC=*C*CO) and δ 165–170 (N*C*=CCO). In the ^1H NMR spectra of **3a**–**d**, the signal observed at δ 9.7–9.75 (1H, s) is consistent with the aldehydic proton, whilst a broad singlet, δ 9.5–10.4 represents the NH. The geometry of the enediamine is shown with the formyl/alkanoyl substituent *syn* (and potentially hydrogen-bonding) to the NH of the heterocyclic ring (N-3), as supported by the ^{13}C NMR chemical shifts of the C=O carbons, see above, and our experience with related structures.[7]

We have further probed the questions of tautomerism and geometry in the solid state by X-ray crystal structure analysis of enediamines **3f** and **3g**. We have previously shown that related enediamine **4** exists in the solid state as the *syn*-enaminoketone form.[7] In the current work, it was found that compound **3f** displays an NH proton and a dihedral angle N-1/C-2/C(α)/



Scheme 1

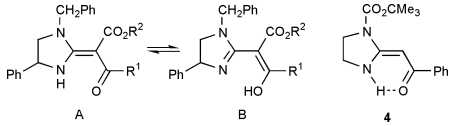


Fig. 1 Tautomerism of enediamines **3**.

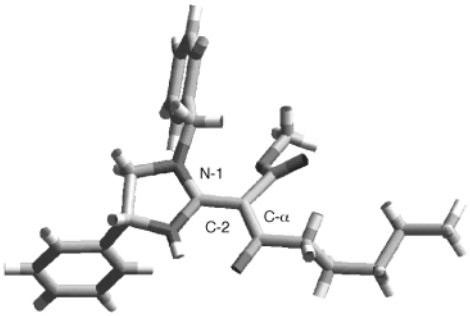


Fig. 2 X-Ray crystal structure of enediamine **3f**.

CO_2Me of 21° (Fig. 2).† This near-planarity suggests that hydrogen bonding is operating from N-3(H) to the keto-carbonyl group, consistent with the enaminoketone tautomer in the solid state. On the other hand, compound **3g** reveals two independent molecules in the unit cell, dihedral angles N-1/C-2/C(α)/CO_2Me of 100° (Fig. 3) and 113°, with some alkyl chain conformational differences.† These large deviations from planarity, precluding a C-2,C(α) double bond, and the location of a proton on oxygen rather than N-3 (Fig. 3), imply that the hydrogen bonding is absent and that the imino–enol tautomer B is present in this instance.

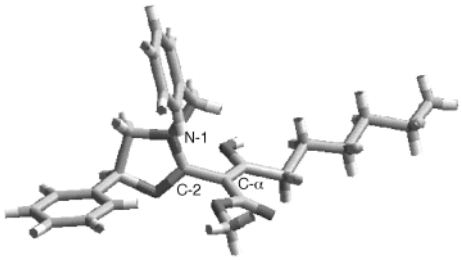
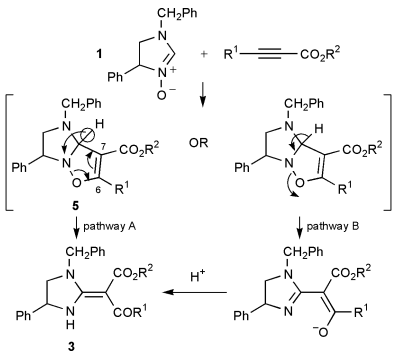


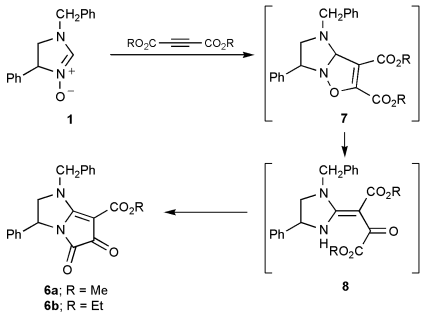
Fig. 3 X-Ray crystal structure of enediamine **3g**; two independent molecules per unit cell.

The formation of the enediamine **3** can be best rationalised through N–O cleavage of the expected imidazoisoxazole products **5** of an initial 1,3-dipolar cycloaddition of nitrone **1** (Scheme 3). Two possibilities can then be envisaged, pathways A and B of Scheme 3. Pathway A postulates a sigmatropic 1,5-H shift of the bridgehead hydrogen atom and bond reorganisation that would not be possible for the cycloadducts of alkene dipolarophiles (Scheme 1). Alternatively, pathway B suggests loss of the bridgehead proton and N–O bond cleavage, followed by reprotonation.[5] This elimination has a triply stabilised enolate as a leaving group, which would not be the case in the cycloadducts formed from alkenes.

A further unexpected reaction was observed when alkyne-1,2-dicarboxylates were reacted with nitrone **1**. Using dimethyl



Scheme 3



Scheme 4

or diethyl butyn-1,4-dioates, the 2,3,5,6-tetrahydro-1*H*-pyrrolo[1,2-*a*]imidazole-5,6-diones **6a** and **6b**, respectively, were isolated (58 and 20%), Scheme 4. Again, formation of these bicyclic products can be rationalised by initial dipolar cycloaddition to afford imidazoisoxazoles **7**. N–O cleavage *via* either of the pathways proposed in Scheme 3 would lead to an enediamine intermediate that now carries an electrophilic ester group suitably disposed to permit the secondary recyclisation.[8]

We have thus shown that dihydroimidazolium nitrones **1** undergo 1,3-dipolar cycloaddition with alkyne dipolarophiles, and that the cycloadducts suffer N–O bond cleavage to afford enediamines, and subsequent cyclisation where possible.

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Notes and references

† *Crystal data for* **3f**: $C_{25}H_{30}N_2O_3$, M = 406.51, monoclinic, a = 26.9087(10), b = 6.8778(4), c = 24.9780(10) Å, α = 90, β = 106.211(3), γ = 90°, U = 4438.9(4) Å^3, T = 150(2) K, space group $C2/c$, monochromated Mo-Kα radiation, λ = 0.71073 Å, Z = 8, D_c = 1.217 Mg m^{-3}, $F(000)$ = 1744, colourless needles, dimensions 0.12 × 0.02 × 0.02 mm, μ(Mo-Kα) = 0.080 mm^{-1}, 3.06 < 2θ < 24.00°, 8729 reflections measured, 3468 unique reflections. The structure was solved by direct methods and refined by full-matrix least-squares on F^2. The final cycle (for 301 parameters) converged with wR_2 = 0.1059 (for all data) and R_1 = 0.0662 [$I > 2\sigma(I)$].

Crystal data for **3g**: $C_{26}H_{32}N_2O_3$, M = 420.54, triclinic, a = 9.4057(2), b = 11.341(2), c = 33.051(7) Å, α = 92.243(4), β = 99.513(4), γ = 103.536(4)°, U = 2360.5(3) Å^3, T = 150(2) K, space group $P\bar{1}$, monochromated Mo-Kα radiation, λ = 0.71073 Å, Z = 4, D_c = 1.181 Mg m^{-3}, $F(000)$ = 900, colourless plates, dimensions 0.10 × 0.10 × 0.05 mm, μ(Mo-Kα) = 0.077 mm^{-1}, 3.02 < 2θ < 21.97°, 12951 reflections measured, 5590 unique reflections. The structure was solved by direct methods and refined by full-matrix least-squares on F^2. The final cycle (for 564 parameters) converged with wR_2 = 0.1129 (for all data) and R_1 = 0.0621 [$I > 2\sigma(I)$]. CCDC 182/1759. See http://www.rsc.org/suppdata/cc/b0/b005530l/ for crystallographic files in .cif format.

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