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Unexpected cycloadducts from 1,3-dipolar cycloaddition of 3,4-dehydromorpholine *N*-oxide to *N*-cinnamoyl piperidines—first report of the novel formation of 2:1 cycloadducts

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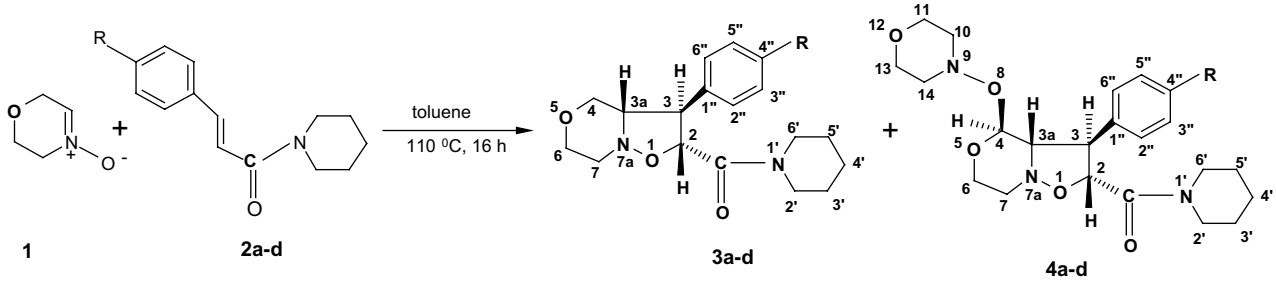
Abstract—A series of unexpected cycloadducts along with normal cycloadducts have been isolated from the 1,3-dipolar cycloaddition of 3,4-dehydromorpholine *N*-oxide to piperidides of cinnamic acid and *para*-substituted cinnamic acids and these were analyzed by X-ray crystallography to reveal novel solid-state structures. At first, 1:1 cycloadducts were formed which underwent in situ nucleophilic attack by another reduced nitrone moiety. A plausible iminium–oxonium ion mechanism has been proposed.

1,3-Dipolar cycloaddition of nitrones to unsubstituted olefins constitutes the best procedure for the construction of isoxazolidines.[1–3] Isoxazolidines, containing two heteroatoms, can be considered as masked forms of several functional group combinations. Thus, nitrone cycloadducts are attractive intermediates for the synthesis of several classes of biologically active compounds as well as natural products.[1–5]

As a part of our investigations in this particular field,[6] we carried out the $\pi^4s + \pi^2s$ cycloaddition reactions of 3,4-dehydromorpholine *N*-oxide **1**, derived from morpholine, with *N*-cinnamoyl piperidine **2a** and three of its *para*-substituted derivatives **2b–d**. As a result, the expected 1:1 cycloadducts **3a–d**, as well as their regio- and stereoisomers were formed in addition to the novel 2:1 cycloadducts **4a–d** comprising two molecules of the nitrone and one molecule of the dipolarophile. Since the nitrone **1** has not previously been utilized in cycloaddition reactions, and since the formation of the novel 2:1 cycloadducts is unprecedented and mechanistically attractive, we briefly present our findings herein.



Scheme 1. For compounds **2–4**: R = H (**a**), Cl (**b**), OMe (**c**), NO_2 (**d**).

Keywords: Nitrone; Dipolar cycloaddition; Intermolecular; Isoxazolooxazines.
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When equimolar amounts of **1** and each of **2a–d** were separately refluxed in anhydrous toluene for 16 h under a dry nitrogen atmosphere, followed by column chromatography over neutral alumina, compounds **4a–d** were isolated[7a–d] as the major products (44–58%) along with the 1:1 cycloadducts **3a–d** (15–22%) and some of their regio- and stereoisomers (Scheme 1).

The ^{1}H NMR spectrum of **4a** showed the presence of twenty-six aliphatic protons, which pointed to the participation of two molecules of the dipolar species and one molecule of the dipolarophile in its formation. Six of these protons appeared between δ 1.43–1.66 which were assigned to H-3′, 4′ and 5′ of the piperidine ring. The twenty other aliphatic protons between δ 2.72–5.04 were either attached to carbons linked to heteroatoms (oxygen/nitrogen) or linked to aryl or carbonyl groups. Extensive ^{1}H–^{1}H decoupling, ^{1}H–^{1}H COSY and ^{1}H–^{1}H TOCSY experiments were conducted. Thus the doublet at δ 4.66 due to H-2 had no long-range correlation with the aromatic protons, while H-3, a triplet at δ 4.47 did. This confirmed that H-3, and not H-2, was benzylic in nature. Hence, the cycloadduct **4a** was a 3-aryl-2-piperidinyloxoisoxazolo [2,3-*a*][1,4]oxazine derivative. The sequence H-2–H-3–H-3a–H-4 was established by double irradiation experiments. The appearance of only one H-4 proton and its lowfield value (compared with that of the corresponding normal adduct) indicated that the 4-oxomorpholine unit was attached through an ether linkage to C-4. The COSY and TOCSY experiments were also in agreement with this inference. The remaining four protons of the piperidine unit, that is, H-2′ and H-6′ could be identified from ^{1}H–^{1}H decoupling and COSY investigations. These, taken in conjunction with the ^{13}C NMR and XHCORR (single-bond) spectra, suggested that these twelve aliphatic protons belonged to six methylene groups in the three remaining OCH_2CH_2N units.

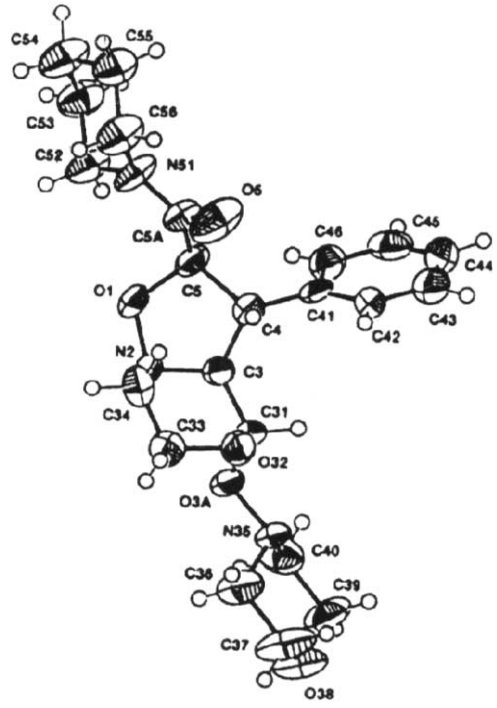
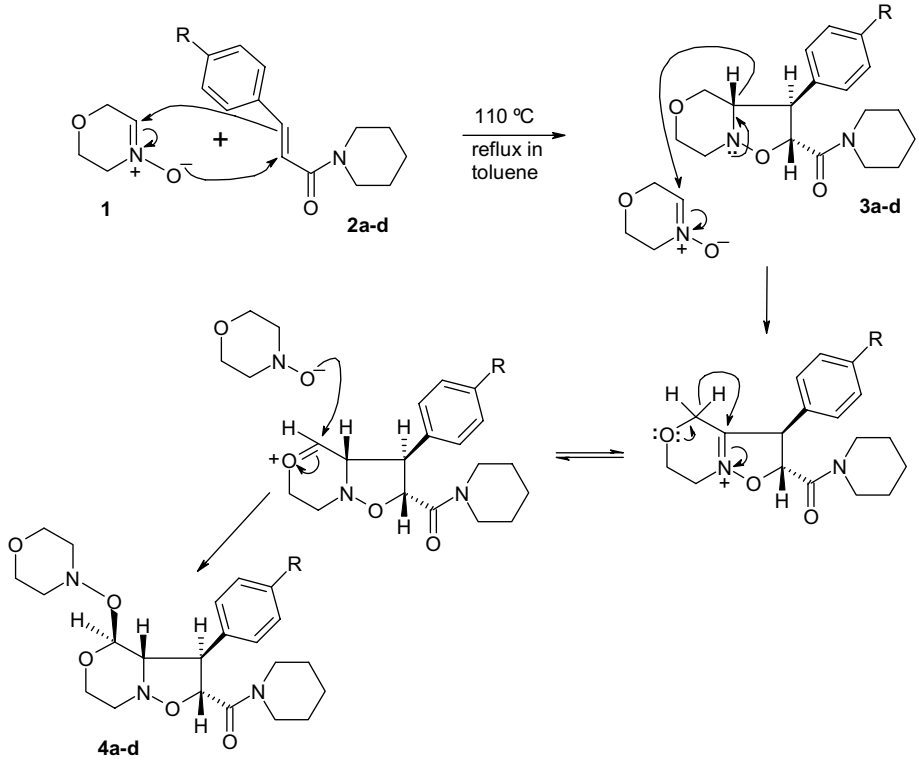


Figure 1. ORTEP projection of **4a**.



Scheme 2.

The ^{13}C NMR spectrum, including APT/DEPT-135°, lent full support to the derived structure. The signal for C-4 resonated much further downfield (δ 98.7) in comparison to that (δ 64.3) in the corresponding normal cycloadduct **3a**.

Although extensive 1D and 2D NMR experiments unveiled the correct regio- and stereostructure of **4a**, the unambiguous structure was finally confirmed by X-ray crystallographic studies. The ORTEP projection[8] (Fig. 1) shows an all *trans* stereochemistry for the chain C(4)–C(3a)–C(3)–C(2).

The N-7a atom is pyramidal (sp^3) with its lone pair *cis* with respect to H-3a, which confirms a *pseudo–cis* junction between the two central rings. The full stereostructures of **4b–d** were also determined by extensive 1D and 2D NMR experiments.

Since compounds **3a–d** bearing the same stereochemistry at C-2, C-3 and C-3a as those in **4a–d** were also isolated along with **4a–d**, we propose the following mechanism (Scheme 2) for the formation of the latter through the intermediacy of the former (Scheme 1). The proposed mechanism[9] for the formation of the unexpected series of products **4a–d** follows an iminium–oxonium pathway. In the first step, the nitrone **1** undergoes 1,3-dipolar cycloadditions with the dipolarophiles **2a–d** to form the corresponding expected cycloadducts **3a–d** along with other cycloadducts of different regio- as well as stereochemistry. The X-ray crystallographic structure (ORTEP projection) of one such *para*-methoxy substituted[7e] cycloadduct **3c** is depicted in Figure 2. In the next step, a second molecule of the nitrone abstracts a hydride from C-3a and is itself reduced. This is followed by hydride transfer from C-4 to C-3a, a process facilitated by the formation of an oxonium ion. Perhaps these two species exist in equilibrium. The final step is nucleophilic attack by the reduced nitrone at C-4 of the oxonium species to yield the final products. Pertinently, the alternative mechanism involving the formation of a new nitrone from two molecules of **1**, followed by its 1:1 cycloaddition with the dipolarophiles, was ruled out because no such product could be traced (TLC or ^1H NMR) in the reaction mixture or isolated therefrom.

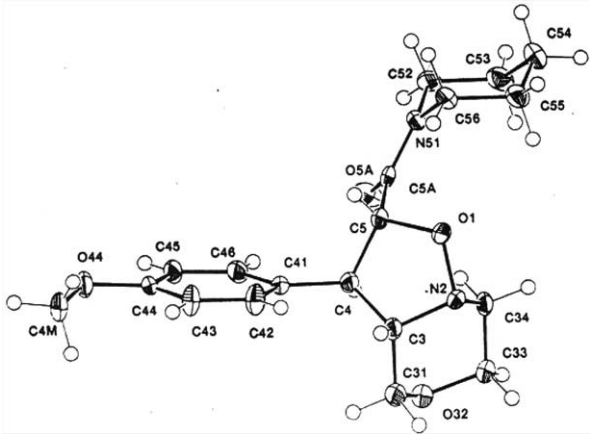


Figure 2. ORTEP diagram of **3c**.

To the best of our knowledge, the present work not only involves the first use of 3,4-dehydromorpholine *N*-oxide as a dipolar species in $\pi^4s + \pi^2s$ cycloaddition reactions but also constitutes the first report of the formation of the cycloadducts resulting from the participation of two molecules of the same dipolar species with dipolarophiles.

Acknowledgements

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7. (a) Spectroscopic data for compound **4a**: (2*RS*,3*SR*,3a*RS*,4*SR*)-2,3,3a,4,6,7-hexahydro-3-phenyl-2-(piperidin-1-ylcarbonyl)-4-(morpholin-1-yloxy)-isoxazolo-[2,3-*a*][1,4]oxazine; mp 168 °C (5% ethyl acetate in benzene, yield 58%); UV (CH_3OH) λ_{max} (nm) (log ε) 208 (4.35); IR (KBr) ν (cm^{-1}) 2927, 2862, 1634, 1244, 1102, 1057, 1019, 753, 674; ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 1.43–1.66 (m, 6H), 2.72 (td, J = 11.1, 2.7 Hz, 1H), 2.82 (td, J = 10.8, 3.0 Hz, 1H), 2.86–3.08 (m, 2H), 3.18 (distorted t, 1H), 3.25–3.30 (m, 2H), 3.49 (m, 1H), 3.50–3.60 (m, 4H), 3.61–3.70 (m, 2H), 3.76–3.85 (m, 2H), 4.01 (dt, J = 7.5, 2.7 Hz, 1H), 4.47 (t, J = 8.4 Hz, 1H), 4.66 (d, J = 7.7 Hz, 1H), 5.04 (d, J = 2.7, 1H), 7.24–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.4, 25.6, 26.4, 43.7, 46.8, 50.7, 51.1, 56.4, 57.9, 58.9, 65.9, 66.1, 69.3, 83.5, 98.7, 127.4, 128.1, 129.0, 139.5, 167.0. EIMS (*m*/*z*): 416 (M^+-1), 330, 315, 229, 215, 214, 201, 130, 112, 99, 84, 77. Anal. Calcd for $C_{22}H_{31}N_3O_5$: C, 63.29; H, 7.48; N, 10.06. Found: C, 63.21; H, 7.37; N, 10.15; (b) Spectroscopic data for compound **4b**: (2*RS*,3*SR*,3a*RS*,4*SR*)-2,3,3a,4,6,7-hexahydro-3-(4″-chlorophenyl)-2-(piperidin-1-ylcarbonyl)-4-(morpholin-1-yloxy)-isoxazolo[2,3-*a*][1,4]oxazine; mp 174 °C (20% ethyl acetate in benzene, yield 51%); UV (CH_3OH) λ_{max} (nm) (log ε) 220 (4.21); IR (KBr) ν (cm^{-1}) 2937, 2854, 1637, 1257, 1102, 1008, 860, 743; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 1.54–1.65 (m, 6H), 2.73 (distorted td, 1H), 2.83 (distorted td, 1H), 3.09–3.14 (m, 2H), 3.17 (distorted td, 1H), 3.22–3.35 (m, 2H), 3.48 (m, 1H), 3.50–3.72 (m, 6H), 3.77–3.86 (m, 2H), 4.00 (m, 1H), 4.47 (t, J = 8.1, 1H), 4.58 (d, J = 7.2,

1H), 5.02 (d, J = 2.8 Hz, 1H), 7.22–7.39 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.5, 25.6, 26.6, 43.8, 46.7, 50.7, 50.9, 56.5, 57.0, 59.2, 66.1 (two carbons), 69.2, 83.6, 98.8, 129.1, 129.5, 132.7, 137.8, 167.0. EIMS (*m*/*z*): 450 (M^+-1), 350, 348, 235, 164, 112, 77. Anal. Calcd for $C_{22}H_{30}N_3O_5Cl$: C, 58.47; H, 6.64; N, 9.30. Found: C, 58.59; H, 6.73; N, 9.03.; (c) Spectroscopic data for compound **4c**: (2*RS*, 3*SR*,3a*RS*,4*SR*)-2,3,3a,4,6,7-hexahydro-3-(4″-methoxyphenyl)-2-(piperidin-1-ylcarbonyl)-4-(morpholin-1-yloxy)-isoxazolo[2,3-*a*][1,4]oxazine; gummy mass (5% ethyl acetate in benzene, yield 49%); IR (KBr) ν (cm^{-1}) 2938, 2857, 1630, 1248, 1180, 1122, 1022, 830, 692; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 1.40–1.56 (m, 6H), 3.05 (distorted t, 1H), 3.09 (distorted t, 1H), 3.24–3.29 (m, 3H), 3.35–3.56 (m, 7H), 3.61–3.69 (m, 3H), 3.75 (s, 3H), 3.80 (distorted t, 1H), 3.85 (distorted t, 1H), 4.48 (t, J = 8.6 Hz, 1H), 4.69 (d, J = 7.8 Hz, 1H), 5.00 (d, J = 2.2 Hz, 1H), 6.63 (d, J = 12.0 Hz, 2H), 7.26 (d, J = 12.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.5, 25.6, 26.2, 43.2, 46.7, 50.6, 52.1, 55.3, 63.7, 65.5, 66.2, 68.2, 84.3, 98.7, 114.6, 129.2, 130.2, 159.1, 167.9. Anal. Calcd for $C_{23}H_{33}N_3O_6$: C, 61.73; H, 7.43; N, 9.39. Found: C, 61.52; H, 7.31; N, 9.44; (d) Spectroscopic data for compound **4d**: (2*RS*, 3*SR*,3a*RS*,4*SR*)-2,3,3a,4,6,7-hexahydro-3-(4″-nitrophenyl)-2-(piperidin-ylcarbonyl)-4-(morpholin-1-yloxy)-isoxazolo[2,3-*a*][1,4]oxazine; gummy mass (10% ethyl acetate in benzene, yield 44%); IR (KBr) ν (cm^{-1}) 2934, 2859, 1636, 1268, 1113, 1011, 853, 751; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 1.32–1.60 (m, 6H), 2.97–3.13 (m, 2H), 3.30 (t, J = 9.3 Hz, 1H), 3.26–3.46 (m, 3H), 3.49–3.66 (m, 6H), 3.73-4.04 (m, 6H), 4.54 (d, J = 7.5 Hz, 1H), 5.01 (d, J = 3.1 Hz, 1H), 7.46 (d, J = 9.0 Hz, 2H), 8.14 (d, J = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.1, 25.7, 26.6, 43.7, 46.7, 50.6, 53.2, 59.4, 61.2, 64.1, 69.9, 84.7, 99.4, 123.6, 126.0, 147.3, 148.7, 167.3. Anal. Calcd for $C_{22}H_{30}N_4O_7$: C, 57.13; H, 6.54; N, 12.11. Found: C, 57.01; H, 6.63; N, 12.08; (e) Spectroscopic data for compound **3c**: (2*RS*,3*SR*,3a*RS*)-2,3,3a,4,6,7-hexahydro-3-(4″-methoxyphenyl)-2-(piperidin-ylcarbonyl)-isoxazolo[2,3-*a*][1,4]oxazine; mp 140 °C (5% ethyl acetate in benzene, yield 22%); UV (CH_3OH) λ_{max} (nm) (log ε) 225 (4.21); IR (KBr) ν (cm^{-1}) 2939, 2866, 1626, 1247, 1124, 830; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 1.41–1.63 (m, 6H), 3.10 (distorted dt, 1H), 3.26 (m, 1H), 3.33 (br dd, 1H), 3.42 (m, 1H), 3.47–3.53 (m, 2H), 3.56 (m, 1H), 3.69 (m, 1H), 3.75 (m, 1H), 3.78 (s, 3H), 3.78–3.81 (m, 1H), 3.90 (distorted dt, 1H), 4.51 (dd, J = 9.5, 8.6 Hz, 1H), 4.71 (d, J = 8.4 Hz, 1H), 6.88 (d, J = 12.2 Hz, 2H), 7.28 (d, J = 12.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.5, 25.6, 26.5, 43.8, 46.8, 48.6, 52.1, 55.3, 63.6, 65.7, 68.3, 84.2, 114.9, 129.7, 130.3, 159.4, 167.9. EIMS (*m*/*z*): 346 (M^+), 330, 246, 234, 161, 133, 121, 112, 84, 77. Anal. Calcd for $C_{19}H_{26}N_2O_4$: C, 65.88; H, 7.56; N, 8.09. Found: C, 66.07; H, 7.37; N, 7.86.

8. Crystal structure data were collected on a Synchrotron LURE diffractometer for both compounds **4a** and **3c**. For compound **4a**, diffraction data were recorded following the rotation method using the Synchrotron beam line W32. The wavelength was set as 0.964 Å, obtained through a Si(1 1 1) curvated monochromator. The detector was an image plate camera (MAR Research 345). The crystal was cooled to −10 °C with FTS equipment. The data consist of 100 frames, 3° rotation each (this corresponds to a 300° rotation range of the crystal). Frames were processed using the HKL suite of programs (DENZO, SCALEPPACK and XPDISP). For the compound **3c**, diffraction data were recorded using Cu-K_α radiation (1.541 Å). The structures were solved by direct methods and refined with isotropic, then anisotropic thermal factors by full-matrix least squares techniques. All hydrogen atoms were calculated at their theoretical places and their positional parameters were refined. Crystallographic data for both the compounds **4a** and **3c**, have been deposited with the Cambridge Crystallographic Data Centre as CCDC 235158 (**4a**) and 235157 (**3c**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail:deposit@ccdc.cam.ac.uk).
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