Formation of 2,6-Bis(4-chlorophenyl)-5,6-dihydro-2*H*-1,3,4-oxadiazine-4-oxide by an Intramolecular Amino/Nitro Dehydration

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For an ongoing synthetic project, we had need of a convenient synthesis of β-nitrostyrenes and were attracted to a recent publication describing the condensation of some electron-rich aldehydes with nitromethane under ultrasound.[2] Electron−neutral aromatic aldehydes and those containing electron-withdrawing substituents were reported to give only the intermediate nitro alcohols. We have confirmed the above results, but in addition have found that by raising the reaction temperature to 60−65 °C, again under ultrasound conditions, nitrostyrenes are the major product with both of the above classes of aldehydes. We report in this paper on a remarkable compound of unprecedented structural type isolated in the course of the above synthetic investigation (Scheme 1).

Condensation of 4-chlorobenzaldehyde with nitromethane (as solvent) in the presence of 2.2 equiv of ammonium acetate and 2.6 equiv of acetic acid under ultrasound irradiation at 60−65 °C for a period of 6 h gave a reaction mixture that showed by TLC the presence of a small amount of the intermediate nitro alcohol **1**, a fast-moving spot of the expected nitrostyrene **2**, and a distinct spot of intermediate R_f representing an unknown reaction product. Separation of the above three compounds was readily achieved by column chromatography, yielding 4−6% of the nitro alcohol **1** (the only product formed under ultrasound conditions at room temperature), 65% of 4-chloro-β-nitrostyrene (**2**), and an oil representing the unknown of intermediate R_f (**3**). Low-resolution mass spectroscopy revealed that **3** had the molecular formula $C_{15}H_{12}Cl_2N_2O_2$. HRMS gave MH^+ = 323.0329 (calcd 323.0354), confirmed by microanalysis. The proton and carbon NMR spectra are also consistent with the above molecular formula. Repetition of the above reaction with 2 equiv of 4-chlorobenzaldehyde and only 1 equiv of nitromethane produced an almost identical reaction mixture. It is remarkable that this byproduct, clearly formed from two moieties of the aldehyde and one moiety of nitromethane, is formed even in the presence of a large excess of nitromethane.

A suite of NMR experiments (1D ^{1}H and ^{13}C, 2D COSY, HMQC, HMBC, and NOESY) were performed, and the results are summarized in Table 1. The COSY spectrum showed that protons *f*, *g*, and *h* could be analyzed into an AMX three-spin system and that protons *b* and *d*, as well as protons *c* and *e*, form two separate two-spin pairs, with $\delta_d > \delta_e$. The HMQC data established the multiciplicity of all carbons, especially the one-bond connectivity between carbon *A* (162.51 ppm) and proton *a* (8.32 ppm).

The most revealing information comes from an analysis of the long-range proton−carbon correlation HMBC spectrum, where all cross-peaks are assigned. The following cross-peaks unequivocally establish certain key connectivities in the six-membered ring skeleton: carbon *A* and proton *f*, *K* and *a*, *C* and *f*, as well as *E* and *a*. Finally, a fast 2D NOE experiment[3] unveiled the through-space proximity of protons *a* and *f*, supporting the depicted three-dimensional conformation. The observation of these cross-peaks implies that the central ring structure is rigid and provides further spectroscopic evidence supporting the elucidated structure **3**. We are unaware of any precedent for the unusual downfield chemical shift for sp^3 carbon *A* (δ 162.5).

It appears that this unusual cyclic structure resulted through dehydration of a penultimate intermediate **7** formed, in turn, from **6** by intramolecular attack on the nitro group by the hemiaminal amino group. This latter intermediate could have arisen either through capture of the initial aldol product **1** by 4-chlorobenzalimine (**5**), formed in situ from 4-chlorobenzaldehyde in the NH_4-OAc/HOAc reaction medium, or by Michael addition of hemiminal **4** to the nitrostyrene **2**. The formation of an azoxy functionality from an amine and a nitro group has been observed previously only in rigid systems such as 2-nitrophenylguanidine, 2-nitrophenylhydrazine, or 2-nitro-2′-aminobiphenyl.[4] Such a reaction is remarkable in the present case, however, because the precursor to ring closure, compound **6**, is flexible, and ring closure of **6** to **7** is probably reversible (the 2,6-diaryl substituents in **3** are clearly cis). Furthermore, strong base is *not* required for the cyclization/dehydration. It should be noted that this azoxy synthesis represents an intriguing redox and regiochemical counterpart to the classical synthesis of this functionality from nitroso compounds and hydroxylamines, with the added feature that it places oxygen on the alternate nitrogen atom. This appears to be the first 1,3,4-oxadiazine system to have been prepared with a nitrogen−nitrogen double bond and one of the very few examples in which a nitrogen−nitrogen bond is formed in the cyclization step.[5]

Attempts to extend this curious reaction to other aldehydes were disappointing. 3-Chlorobenzaldehyde gave a similar mixture of nitrostyrene, nitro alcohol, and dihydrooxadiazine-4-oxide, but a variety of other aromatic aldehydes (benzaldehyde, 2-chlorobenzaldehyde, 2,4-dimethoxybenzaldehyde, 3,4,5-trimethoxybenzaldehyde) gave no detectable amount of dihydrooxadiazine-4-oxide; the only (major and identified) products appeared to be the respective nitrostyrenes and nitro alcohols.

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(2) McNulty, J.; Steere, J. A.; Wolf, S. *Tetrahedron Lett.* **1998**, *39*, 8013.

(3) Wagner, R.; Berger, S. *J. Magn. Reson., Ser. A* **1996**, *123*, 119.

(4) (a) For a discussion and references, see: Katritzky, A. R.; Lagowski, J. M. *Chemistry of the Heterocyclic N−Oxides*; Academic Press: New York, 1971; pp 120−141. (b) Suzuki, H.; Kawakami, T. *Synthesis* **1997**, 855. (c) Suzuki, H.; Kawakami, T. *J. Org. Chem.* **1999**, *64*, 3361.

(5) See: Smalley, R. K. In *Comprehensive Heterocyclic Chemistry II*, Vol. 6; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier Science, Inc.: New York, 1996; pp 737−781.

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Scheme 1

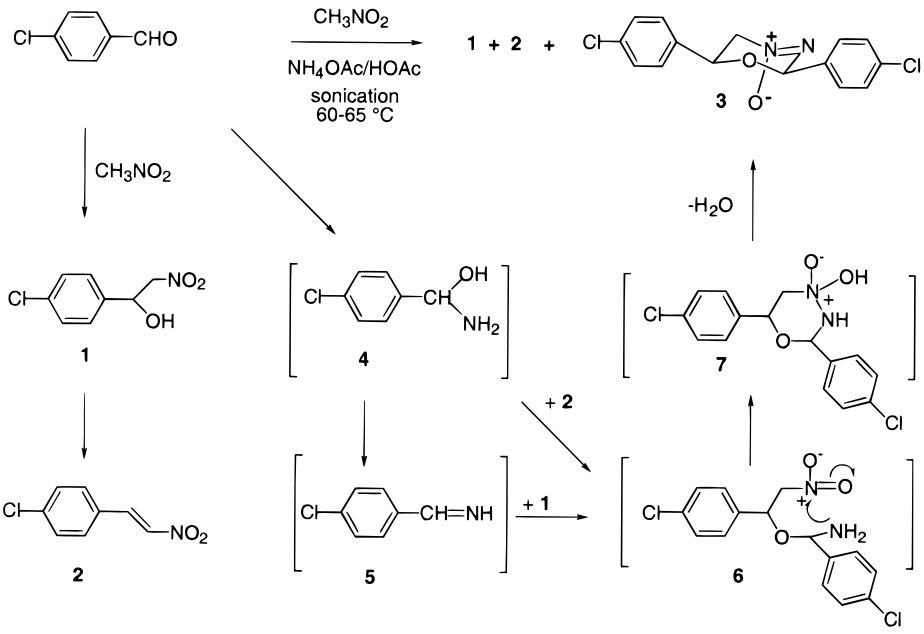
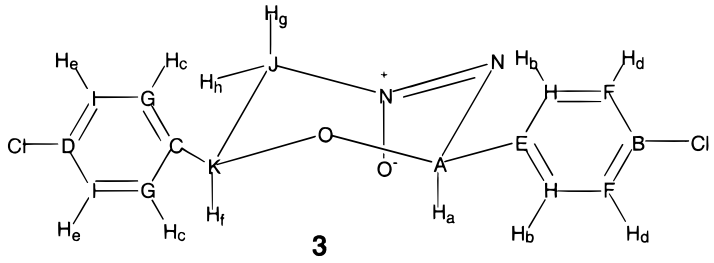


Table 1. Summary of NMR data for 3 ($CDCl_3$, 11.74 T)



^{13} index	^{1}H index	δ_H ppm multiplicity	δ_C ppm	HMBC cross peaks[a]
A	*a*	8.32, s	162.50	$^3J_{Ab}$, $^3J_{Af}$, $^3J_{Ka}$, $^2J_{Ea}$, $^4J_{Fa}$
K	*f*	5.12, dd	70.64	$^3J_{Ka}$, $^3J_{Kc}$, $^2J_{Kg}$, $^2J_{Jf}$, $^4J_{If}$, $^2J_{Cf}$, $^3J_{Af}$
J	*g*	4.89, dd		
	h	4.69, dd	80.54	$^2J_{Jf}$, $^2J_{Kg}$, $^3J_{Cg}$
E			133.65	$^2J_{Ea}$, $^3J_{Ed}$
H	*b*	7.71, d	128.82	$^3J_{Ab}$, $^3J_{Bb}$, $^2J_{Fb}$, $^2J_{Hd}$
F	*d*	7.38, d	129.75	$^4J_{Fa}$, $^2J_{Fb}$, $^2J_{Hd}$, $^3J_{Ed}$, $^2J_{Bd}$
B			137.40	$^3J_{Bb}$, $^2J_{Bd}$
C			136.65	$^2J_{Cf}$, $^3J_{Cg}$
G	*c*	7.44, d	129.12	$^2J_{Ge}$, $^3J_{Kc}$
I	*e*	7.38, d	128.46	$^2J_{Ic}$, $^4J_{If}$
D			134.17	$^2J_{Dc}$

[a] J_{xy} denote the long range ($n = 2-4$) ^{13}C and ^{1}H coupling constants between carbon *X* and proton *y*.

4-Nitrobenzaldehyde gave what appeared from NMR data to be the corresponding dihydrooxadiazine-4-oxide (in 7.2% yield), but this compound proved to be too unstable for reliable characterization. Several representative aliphatic aldehydes (pentanal and 3-phenylpropionaldehyde) under the above conditions failed to give identifiable products.

Experimental Section

2,6-Bis(4-chlorophenyl)-5,6-dihydro-2*H*-1,3,4-oxadiazine-4-oxide (3). A mixture of 4-chlorobenzaldehyde (2.82 g, 20 mmol), ammonium acetate (3.34 g, 43.4 mmol), acetic acid (3.15 g, 3.3 mL, 52.4 mmol), and nitromethane (13 mL) was sonicated at 60−65 °C. After 6 h, the reaction mixture was poured into 250 mL of ethyl acetate. The resulting organic solution was washed with water, dried over Na_2SO_4, and then concentrated. The residue was purified by column chromatography (silica gel/hexane:ethyl acetate = 8:1) to give 2-nitro-1-(4′-chlorophenyl)-ethanol[2,6] (**1**) as a yellow oil (0.24 g, 6% yield; ^{1}H NMR ($CDCl_3$) δ 7.37 (4H, AB), 5.43 (1H, dd, J = 9.5 and 3.0 Hz), 4.57 (1H, dd, J = 13.5 and 9.5 Hz), 4.48 (1H, dd, J = 13.5 and 3.0 Hz), 3.18 (1H, br s); ^{13}C NMR ($CDCl_3$) δ 136.72, 134.90, 129.32, 127.50, 81.11, 70.44), 4-chloro-β-nitrostyrene (**2**) as pale yellow needles, mp 111.5−112.5 °C (lit.[7] mp 111−112 °C) (2.39 g, 65% yield; ^{1}H NMR ($CDCl_3$) δ 7.95 (1H, d, J = 14.0 Hz), 7.56 (1H, d, J = 14.0 Hz), 7.49 (2H, d, J = 8.5 Hz), 7.42 (2H, d, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 138.53, 137.88, 137.63, 130.46, 129.97, 128.74), and **3** (0.50 g, 15.5% yield: ^{1}H NMR ($CDCl_3$) δ 8.32 (1 H, s), 7.71 (2 H, d, J = 8.5 Hz), 7.44 (2 H, d, J = 8.5 Hz), 7.38 (4 H, d, J = 8.5

(6) Bernasconi, C. F.; Paschalis, P. *J. Am. Chem. Soc.* **1989**, *111*, 5893.

(7) Mouhtaram, M.; Jung, L.; Stambach, J. F. *Tetrahedron* **1993**, *49*, 1391.

Hz), 5.12 (1 H, dd, $J = 10.0$ and 4.0 Hz), 4.89 (1 H, dd, $J = 12.5$ and 10.0 Hz), 4.69 (1 H, dd, $J = 12.5$ and 4.0 Hz); ^{13}C NMR ($CDCl_3$) δ 162.50, 137.40, 136.65, 134.17, 133.65, 129.75, 129.12, 128.82, 128.46, 80.54, 70.64; MS *m*/*z* 323 (MH^+) 288, 275, 262, 240, 227, 214, 199, 191, 183, 165, 150, 138, 125, 111, 103, 89, 75; HRMS calcd for $C_{15}H_{13}Cl_2N_2O_2$ (MH^+) 323.0354, found 323.0329. Anal. Calcd for $C_{15}H_{12}Cl_2N_2O_2$: C, 55.75, H, 3.74, N, 8.67. Found: C, 55.29, H, 3.78, N, 8.40.

2,6-Bis(3-chlorophenyl)-5,6-dihydro-2*H*-1,3,4-oxadiazine-4-oxide. This compound was isolated in 14.2% yield as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 8.33 (1H, s), 7.84 (1H, t, $J = 1.5$ Hz), 7.63 (1H, dt, $J = 7.5$ and 1.5 Hz), 7.57−7.48 (1H, m), 7.46−7.39 (1H, m), 7.38−7.33 (4H, m), 5.13 (1H, dd, $J = 10.5$ and 4.0 Hz), 4.91 (1H, dd, $J = 12.5$ and 10.5 Hz), 4.70 (1H, dd, $J = 12.5$ and 4.0 Hz); ^{13}C NMR ($CDCl_3$) δ 162.93, 140.19, 137.09, 135.16, 135.06, 131.74, 130.58, 130.11, 128.97, 128.35, 127.57, 127.41, 125.49, 80.73, 71.09; EIMS *m*/*z* 323 (MH^+), 304, 288, 275, 240, 227, 199, 183, 165, 151, 138, 125, 111, 103, 89, 75; HRMS calcd for $C_{15}H_{13}Cl_2N_2O_2$ (MH^+) 323.0354, found 323.0359.

Supporting Information Available: Spectral data for compound **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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