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Tandem nitrosation/cycloaddition of heterocyclic enamines using nitrolic acids

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ABSTRACT

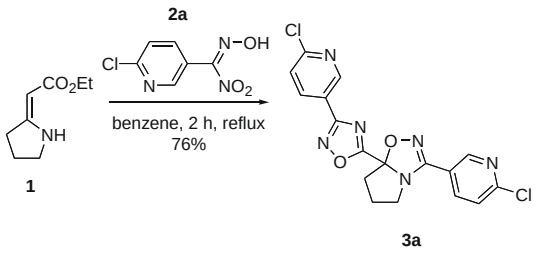
The reaction of alkylidenepyrrolidines with nitrolic acids gives rise to the formation of novel 3,7a-disubstituted (1,2,4-oxadiazol-5-yl)-5,6,7,7a-tetrahydropyrrolo[1,2-*d*][1,2,4]oxadiazoles. A plausible mechanism for this reaction is proposed, which features nitrosation of the enamine by the nitrous acid that is liberated from the nitrolic acid.

Nitrile oxides are versatile 1,3-dipoles, undergoing cycloaddition reactions with a wide range of alkenes and alkynes.[1] They are generally prepared by treatment of hydroxamic acid chlorides with base, or by oxidation of aldoximes. Elimination of HNO_2 from nitrolic acids has also been reported as a route to nitrile oxides, which were subsequently trapped in cycloaddition reactions with alkenes,[2] although this method has not seen widespread application. In particular, reactions of nitrolic acids with electron-rich alkenes such as enamines remain unexplored. The Elliott group has a long-standing interest in the chemistry of alkylidenepyrrolidines,[3] and the Dürüst group in dipolar cycloaddition chemistry,[4] and as such we decided to investigate the reactions of nitrile oxides with this class of alkene.

Reaction of nitrolic acid **2a**, prepared by nitration of the corresponding aldoxime, with alkylidenepyrrolidine **1** gave a single product in high yield. The structure of the product was eventually elucidated by single crystal X-ray diffraction (Fig. 1), with the structure **3a** (Scheme 1) being entirely supported by ^1H and ^{13}C NMR data as well as infrared spectroscopy and mass spectrometry.[5]

This transformation is extremely intriguing. The alkylidenepyrrolidine ester appears to have undergone hydrolysis/decarboxylation, which is unusual under such mild conditions. Two equivalents of the nitrolic acid have been incorporated, with one of them appearing to retain the nitrogen of the nitro group. Although we are unable to give a definitive mechanism, the following (Scheme 2) is plausible, and is supported by some experimental data (vide infra). The nitrous acid which is lost upon heating compound **2a** is trapped by the alkylidenepyrrolidine, giving nitrosoalkene **4** or its oxime tautomer **5**. The decarboxylation of oximinocarboxylic acid has precedent, albeit on the corresponding *O*-acyl compounds.[6] Presumably the presence of the oxime will render the ester more susceptible to hydrolysis, so that while the details are unclear, formation of nitrile **6** is not unreasonable (ester hydrolysis/decarboxylation to give the aldoxime, followed by nitrile oxide cycloaddition/dehydration is also a possibility[7]). From this point, cycloaddition of the nitrile oxide **7** involving the nitrile[8] and imine[9] bonds will give the observed product.

We sought to explore the generality of this process, and also to provide support for the above mechanism. Three other nitrolic acids were used in the above reaction. In all cases, the reactions were more sluggish, but could be accelerated by microwave heat-



Scheme 1.

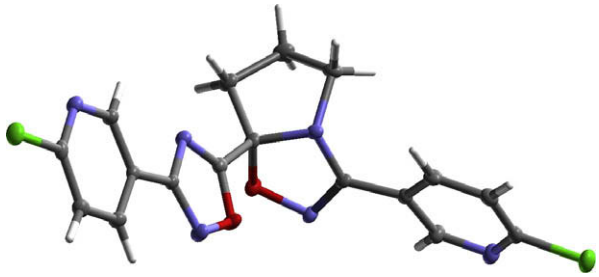


Figure 1. Structure of compound **3a** from single crystal X-ray data.

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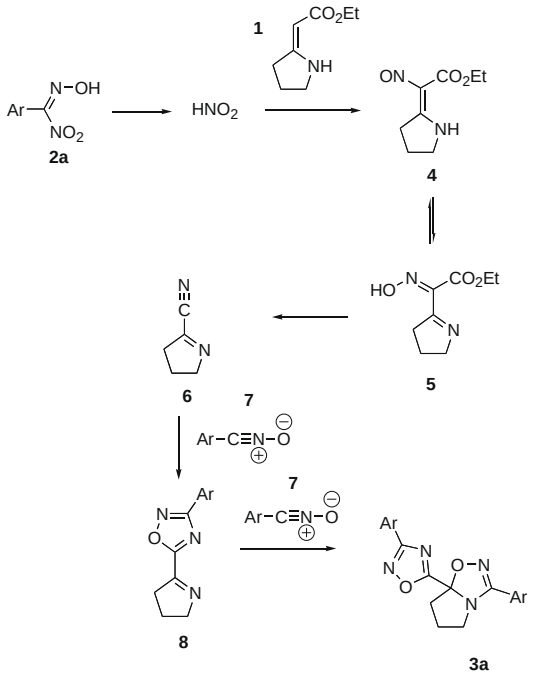


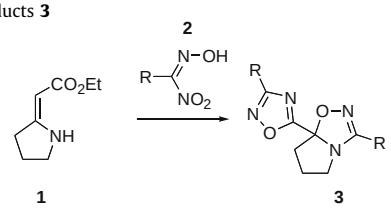
Scheme 2.

ing to provide similar products in good yields (Table 1). In all cases, complete consumption of the alkylidenepyrrolidine reagent **1** was observed.

Variable amounts of a by-product were observed in the ^{1}H NMR data of the crude reaction mixtures. Under milder conditions than those shown in Table 1, this became a significant side-product, and appeared to be consistent with either structure **4** or **5**. Upon chromatography, compound **5** was obtained (^{1}H NMR, ^{13}C NMR, IR, MS).[10] This was similar, but not identical to the compound that we had observed in the crude reaction mixtures, which we would therefore attribute to compound **4** (Scheme 3). In particular, the oxime carbon in compound **5** resonates at 143.2 ppm, whereas the corresponding carbon in alkylidenepyrrolidine **1** resonates at 76.5 ppm. Nitrosation of the alkene, as in compound **4**, is unlikely to lead to such a dramatic increase, whereas related α-oximinoesters show almost identical chemical shifts.[11] Reaction of phenylnitrolic acid only gave compounds **4**/**5**, with compound **3** not observed even under forcing conditions.

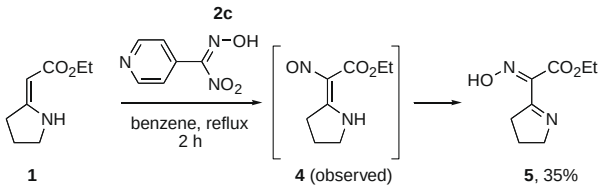
This reaction represents, to the best of our knowledge, the first example of the chemical trapping of nitrous acid liberated from a nitrolic acid, although there are reports of biological studies in which nitrolic acids are used as NO_2/NO sources.[12] The electron-

Table 1
Formation of adducts **3**



Compound	R	Conditions	Yield (%)
3a	6-Chloro-3-pyridyl	Benzene, reflux, 2 h	76
3b	3-Pyridyl	110 °C, 100 W, 10 min[a]	66
3c	4-Pyridyl	110 °C, 100 W, 10 min[a]	58
3d	Me	Toluene, reflux, 2 h	65

[a] CEM discover microwave reactor.



Scheme 3.

rich double-bond of the alkylidenepyrrolidine clearly renders this a 'special case', although we would anticipate many other instances in which the nitrous acid would be trapped. This may therefore limit the applicability of nitrolic acids as nitrile oxide precursors.

Acknowledgements

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References and notes

1. Feuer, H. *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*; John Wiley & Sons: New Jersey, 2008; Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*; John Wiley & Sons: New York, 1984; Easton, C. J.; Hughes, C. M. M.; Savage, G. P.; Simpson, G. W. *Adv. Heterocycl. Chem.* **1994**, *60*, 261–327; Houk, K. N.; Sims, J.; Duke, R. E., Jr.; Strozier, R. W.; George, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 7287–7301; Wagner, G.; Danks, T. N.; Vullo, V. *Tetrahedron* **2007**, *63*, 5251–5260; Vullo, V.; Danks, T. N.; Wagner, G. *Eur. J. Org. Chem.* **2004**, 2046–2052.
2. Matt, C.; Gissot, A.; Wagner, A.; Mioskowski, C. *Tetrahedron Lett.* **2000**, *41*, 1191–1194.
3. Elliott, M. C.; Wood, J. L.; Wordingham, S. V. *Trends Heterocycl. Chem.* **2005**, *10*, 73–95; Elliott, M. C.; Wordingham, S. V. *Synthesis* **2006**, 1162–1170; Davies, C. D.; Elliott, M. C.; Wood, J. L. *Tetrahedron* **2006**, *62*, 11158–11164.
4. Altuğ, C.; Dürüst, Y. A new route for the synthesis of phenyl sulfonyl substituted isoxazoles, International Conference on Organic Chemistry, June 5–9, **2007**, Erzurum, Turkey.
5. *3-(6-Chloropyridin-3-yl)-7a-[3-(6-chloropyridin-3-yl)-1,2,4-oxadiazol-5-yl]-5,6,7,7a-tetrahydropyrrolo[1,2-d][1,2,4]oxadiazole* (**3a**). 6-Chloropyridin-3-nitrolic acid (**2a**) (2.0 equiv, 201 mg, 1.0 mmol) was added to ethyl (2-pyrrolidin-2-ylidene acetate (**1**) (77.5 mg, 0.5 mmol) in dry benzene (10 mL) and the mixture was heated at reflux for 2 h. The reaction mixture was concentrated in vacuo, and the crude residue was purified by flash column chromatography (1: 1 petroleum ether–ethyl acetate) to give the *title compound* (154 mg, 76%) as a yellow solid, m.p. 162–163 °C; $\nu_{max.}$ (Nujol) 1582, 1555, 1141, 1114, 967, 933, 893, 838, 722 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 9.03 (1H, d, *J* 1.8 Hz), 8.71 (1H, d, *J* 1.8 Hz), 8.27 (1H, dd, 8.3, 2.4 Hz), 8.02 (1H, dd, *J* 8.4, 2.4 Hz), 7.41–7.36 (2H, m), 3.43–3.40 (2H, m), 2.88 (1H, ddd, *J* 14.2, 10.7, 6.9 Hz), 2.72 (1H, ddd, *J* 14.2, 7.1, 3.3 Hz), 2.15–2.07 (1H, m), 2.05–1.98 (1H, m); δ_C (100 MHz; $CDCl_3$) 178.2 (C), 166.3 (C), 156.8 (C), 154.7 (C), 154.5 (C), 149.3 (CH), 149.2 (CH), 138.3 (CH), 137.9 (CH), 125.2 (CH), 125.1 (CH), 122.0 (C), 121.1 (C), 104.4 (C), 54.1 (CH_2), 37.7 (CH_2), 25.6 (CH_2); *m/z* (TOF ES$^+$) 444.1 (MH^+ + CH_3CN, 100%), 405.0 (M^+, 16), 403.0 (M^+, 25). *Selected crystallographic data*: $C_{17}H_{12}Cl_2N_6O_2$, FW = 403.23, *T* = 150(2) K, λ = 0.71073 Å, monoclinic, *P*21/*c*, *a* = 6.8900(3) Å, *b* = 13.7810(5) Å, *c* = 18.1120(9), β = 94.5030(10)°, *V* = 1714.45(13) Å^3, *Z* = 4, $\rho_{(calc)}$ = 1.562 Mg/m^3, crystal size = 0.50 × 0.12 × 0.12 mm^3, reflections collected = 6624, independent reflections = 3885, $R_{(int)}$ = 0.0569, parameters = 244, R_1 [$I > 2\sigma(I)$] = 0.085, wR_2 [$I > 2\sigma(I)$] = 0.19, R_1 (all data) = 0.12, wR_2 (all data) = 0.21. Full crystallographic data for this compound have been deposited with the CCDC, reference number 731459, and can be obtained free of charge via http://www.ccdc.cam.ac.uk/data_request/cif.
6. Kim, H. Y.; Lantrip, D. A.; Fuchs, P. L. *Org. Lett.* **2001**, *3*, 2137–2140.
7. Fetizon, M.; Golfier, M.; Milcent, R.; Papadakis, I. *Tetrahedron* **1975**, *31*, 165–170.
8. Diaz-Ortiz, A.; de la Hoz, A.; Alcazar, J.; Carrillo, J. R.; Herrero, M. A.; Fontana, A.; de Mata Munoz, J. *Comb. Chem. High Throughput Screening* **2007**, *10*, 163–169.
9. Risitano, F.; Grassi, G.; Foti, F.; Rotondo, A. *Tetrahedron* **2001**, *57*, 7391–7393; Miller, D. J.; Scrowston, R. M.; Kennewell, P. D.; Westwood, R. *Tetrahedron* **1994**, *50*, 5159–5168; Malamidou-Xenikaki, E.; Coutouli-Argyropoulou, E. *Tetrahedron* **1990**, *46*, 7865–7872.

10. *Ethyl 2-(3,4-dihydro-2H-pyrrol-5-yl)-2-(hydroxyimino)acetate* (**5**). Pyridin-4-nitrolic acid (**2c**) (334 mg, 2 mmol) was added to ethyl (2-pyrrolidin-2-ylidene acetate (**1**) (155 mg, 1 mmol) in dry benzene (10 mL) and the mixture was heated to reflux for 2 h. The reaction mixture was concentrated in vacuo, and the crude residue was purified by flash column chromatography (2:1 petroleum ether–ethyl acetate) to give the *title compound* (65 mg, 35%) as a yellow oil; $\nu_{max.}$ (Nujol) 3000, 1740, 1609, 1473, 1380, 1206 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 4.33 (2H, q, *J* 7.1 Hz, OCH_2), 3.89 (2H, t, *J* 7.7 Hz, NCH_2), 3.14 (2H, t, *J* 8.1 Hz, CH_2), 1.97 (2H, app. quintet, *J* 7.9 Hz, CH_2), 1.33 (3H, t, *J* 7.1 Hz, CH_3); δ_C (100 MHz; $CDCl_3$) 167.9 (C), 164.7 (C), 143.2 (C), 61.4 (CH_2), 54.6 (CH_2), 36.1 (CH_2), 19.7 (CH_2), 14.3 (CH_3); *m/z* (TOF AP^+) 185.1 (MH^+, 100%), 152.1 (38).

11. Lu, J.-Y.; Arndt, H.-D. *J. Org. Chem.* **2007**, *72*, 4205–4212. also see Ref. 6.
12. Oresmaa, L.; Kotikoski, H.; Haukka, M.; Salminen, J.; Oksala, O.; Pohjala, E.; Moilanen, E.; Vapaatalo, H.; Vainiotalo, P.; Aulaskari, P. *J. Med. Chem.* **2005**, *48*, 4231–4236.