Novel Heterocycles: A Convenient Synthesis of the Pyrazolo [3,4-*d*]isoxazole Ring System

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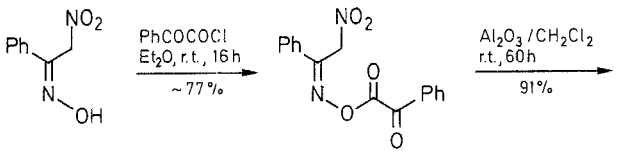
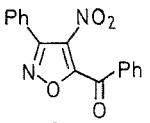
Treatment of the nitroisoxazole **3** with varying amounts of diazomethane afforded, besides compound **5**, the pyrazolo[3,4-*d*]isoxazole derivatives **9** and **10**, respectively. A possible mechanism for the formation of these products, involving the primary cycloadduct **4**, is proposed.

We have recently shown that ethyl 4-nitro-3-phenylisoxazole-5-carboxylate, easily available from α-nitroacetophenone oxime **(1)**,[1] reacted smoothly with diazoalkanes affording 1,5-difunctionalized 2-oxa-3-azabicyclo[3.1.0]hex-3-ene derivatives.[2] In continuation of our interest in the chemistry of strongly electron-deficient isoxazoles, we decided to investigate the behavior of the hitherto unknown nitroketone **3** towards diazomethane. Compound **3** was prepared in 70% yield by reaction of the same nitrooxime **1** with benzoylformyl chloride, followed by base-catalyzed cyclodehydration of the intermediate acyl oxime **2**.



1 **2**



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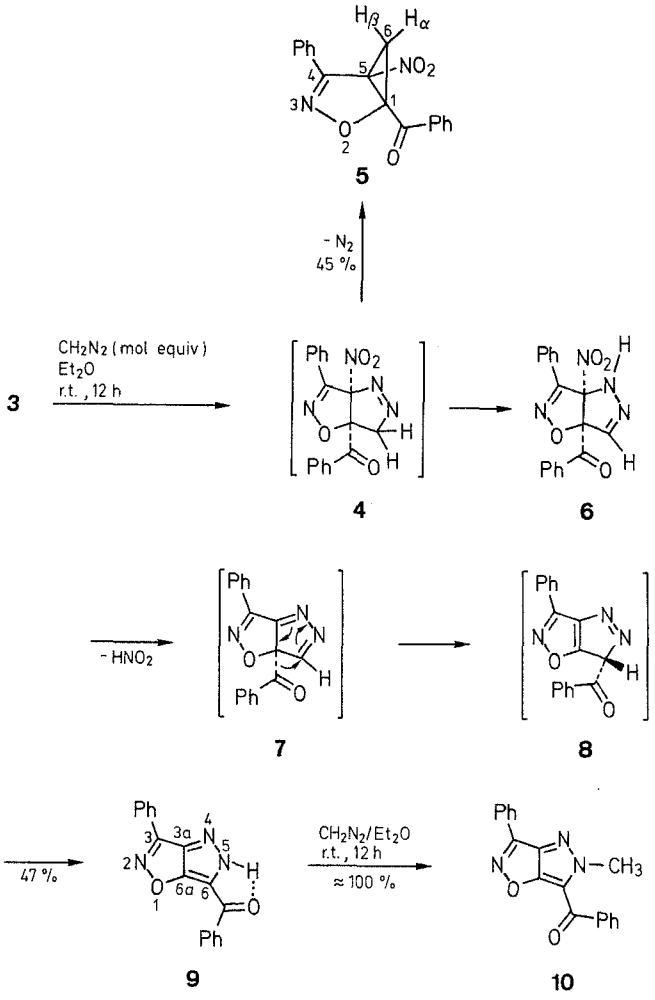
When the nitroisoxazole **3** was allowed to react with an equimolecular amount of diazomethane in ether at room temperature, and the resulting reaction mixture was resolved by flash chromatography, the bicyclic cyclopropane derivative **5** and the new ring system **9** were isolated in 45 and 47% yields, respectively, based on the recovered starting material.

The formation of **5**, whose structure follows from analytical and spectral evidence (Table), can be accounted for on the basis of a regioselective, 1,3-dipolar cycloaddition of the diazoalkane on the C(4)–C(5) isoxazole double bond of **3** (see below), followed by loss of nitrogen from the unstable Δ^1-pyrazoline **4**. A competitive tautomerization of the primary cycloadduct **4** into **6** can be invoked in order to rationalize the isolation of the second product **9**.

Although repeated attempts to isolate the nitroderivative **6** were unsuccessful, the presence of this unstable intermediate in the original reaction mixture was firmly established by diagnostic spectral data (Table), which are in full agreement with the proposed structure. The disappearance of the above compound during the chromatographic work-up of the row product is probably due to the loss of nitrous acid with formation of the bicyclic isopyrazole **7**, which in turn can give rise to the stable pyrazolo-isoxazole **9** through the pyrazolenine **8**. The conversion of **7** into **8**, characterized by a [1,5] sigmatropic shift of the



benzoyl group, closely resembles a Van Alphen–Hüttel rearrangement, well known in the pyrazole chemistry.[3] Treatment of **9** with diazomethane gave the corresponding *N*-methyl derivative **10** quantitatively.

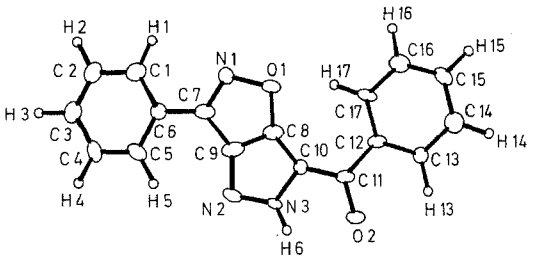


Figure. Molecular structure of 6-benzoyl-3-phenyl-5*H*-pyrazolo[3,4-*d*] isoxazole **(9)** according to X-ray analysis. $C_{17}H_{11}N_3O_2$: Monoclinic, space group $P2_1/n$, a = 5.119(2), b = 9.817(2), c = 26.949(9) Å, $\beta = 94.05(3)°$, v = 1350.92 Å^3, Z = 4, $D_c = 1.422$ g cm^{-3}, $\mu = 0.57$ cm^{-1}. 2558 Unique reflections were measured (at room temperature) on a CADA four-circle diffractometer using Mo-K_α monochromatized radiation ($\lambda = 0.7107$ Å), $\theta/2\theta$ scan mode to a $\theta = 25°$. 1201 Reflections were considered observed with $I > 3\sigma$ (I). The structure was solved by direct methods (SHELX). Full-matrix least squares were used for the refinement, anisotropic for all the non-hydrogen atoms. The hydrogen atoms, except for that linked to nitrogen which has been found in a ΔF synthesis, were introduced in calculated positions. The final R value was 0.088.

When the nitroketone **3** was reacted with an excess of diazomethane, compound **10** was obtained directly in 53% yield, together with a minor amount of **5**, which appears rather unstable under these conditions. The starting material was now fully consumed and no intermediate **6** was detected in the reaction mixture, which contained **10** as the largely predominant product. These features can be explained on the basis of the same

Table. Compounds **2**, **3**, **5**, **6**, **9**, **10** Prepared

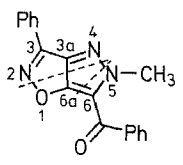
Product	Yield (%)	mp (°C)	Molecular Formula[a]	IR (medium) ν(cm^{-1})	^{1}H-NMR (CDCl$_3$/TMS) δ, J(Hz)	^{13}C-NMR (CDCl$_3$/TMS) δ
2	–[b]	–[b]	$C_{16}H_{12}N_2O_5$ (312.3)	1775 (O–CO); 1685 (Ph–CO); 1560, 1370 (NO_2) (film)	5.79 (s, 2H, CH_2); 7.35–7.80 (m, 8H$_{arom}$); 7.95–8.15 (m, 2H$_{arom}$)	69.1 (t, CH_2); 127.0, 128.0, 128.7, 129.0, 129.6, 131.8, 132.0, 135.3 (C$_{arom}$); 155.4 (s, C=N); 161.1 (s, OCO); 187.4 (Ph–CO)
3	70	71	$C_{16}H_{10}N_2O_4$ (294.3)	1680 (CO); 1530, 1365 (NO_2) (KBr)	7.45–7.85 (m, 8H$_{arom}$); 7.95–8.10 (m, 2H$_{arom}$)	124.1, 128.6, 128.7, 129.0, 129.6, 131.1 (C$_{arom}$); 131.6 (s, C-4); 133.5, 135.5 (C$_{arom}$); 156.6 (s, C-3); 164.7 (s, C-5); 180.5 (CO)
5	45	106–106.5	$C_{17}H_{12}N_2O_4$ (308.3)	3100 (CH_2); 1690 (CO); 1562, 1345 (NO_2) (KBr)	1.65 (d, 1H, J = 7.5, H$_\beta$-6); 3.50 (d, 1H, J = 7.5, H$_\alpha$-6); 7.40–7.85 (m, 8H$_{arom}$); 7.92–8.10 (m, 2H$_{arom}$)	19.35 (dd, C-6); 79.8 (s, C-5); 83.1 (s, C-1); 125.5, 127.0, 128.6, 129.2, 129.6, 131.7, 134.0, 134.5 (C$_{arom}$); 156.95 (s, C-4); 187.7 (s, CO)
6[c]	–[b]	–[b]	$C_{17}H_{12}N_4O_4$ (336.3)	3400 (NH); 1690 (CO) (CCl_4)	7.06 (s, 1H, H-6)	109.4 (s, C-3a/C-6a); 116.5 (s, C-6a/C-3a); 140.3 (d, C-6); 153.0 (s, C-3); 189.1 (s, CO)
9	47	187–188	$C_{17}H_{11}N_3O_2$ (289.3)	3240 (NH); 1635 (CO) (KBr)	7.52–7.74 (m, 7H, 6H$_{arom}$, NH); 8.20–8.32 (m, 4H$_{arom}$)	124.7 (br s, C-3a/C-6); 126.1, 127.3, 128.7, 129.1, 129.4, 131.4, 133.5, 136.1 (C$_{arom}$); 140.25 (br s, C-6/C-3a); 149.8 (s, C-3); 157.4 (br s, C-6a); 182.4 (s, CO)[d]
10[e]	53	162	$C_{18}H_{13}N_3O_2$ (303.3)	1651 (CO) (KBr)	4.51 (s, 3H, NCH_3); 7.45–7.70 (m, 6H$_{arom}$); 8.0–8.35 (m, 4H$_{arom}$)	42.7 (q, NCH_3); 119.5 (s, C-6); 126.5, 127.6, 128.65, 128.9, 130.95, 133.5, 137.1 (C$_{arom}$); 141.8 (s, C-3a); 151.5 (s, C-3); 155.35 (s, C-6a); 182.1 (s, CO)

[a] Apart from the intermediates **2** and **6**, which were not isolated, satisfactory microanalyses were obtained: C ±0.29, H ±0.06, N ±0.3.
[b] Not isolated.
[c] The most diagnostic data of this intermediate were obtained from the spectra of the original reaction mixture.
[d] The ^{13}C-NMR spectrum was recorded in DMSO-d_6.
[e] MS (70 eV): m/z = 303 (M$^+$, 65); 302 (46); 275 (2); 274 (12); 146 (1); 129 (5); 118 (2); 106 (13); 105 (B); 77 (77); 51 (18).

mechanism reported above, since the excess of diazoalkane can favor both the elimination of nitrous acid from **6** and the final conversion of **9** into **10**.

The structure of the tautomerizable compound **9**, suggested by the spectral properties (Table), was unambiguously determined by an X-ray analysis,[4] which showed that it exists in the solid state in the 'chelated' 5-NH form. The same analysis allowed us to confirm the selectivity of the original cycloaddition process for which, according to the behavior of other nitroheterocycles[5] and variously substituted nitroalkenes,[6] the nitro group at position 4 exerts a complete regiochemical control.

Finally, although the alternative regioisomer **11** cannot be definitively ruled out on the basis of the spectral data reported in the Table, the structure **10** appears to be preferred: in fact, the MS spectrum exhibits two peaks at $m/z = 129$ and 146 for the species $C_8H_5N_2$ and C_9H_8NO, respectively, which can arise from **10** according to the fragmentation pattern marked in structure **10**.



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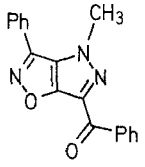

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Melting points were determined on a Büchi 510 apparatus and are uncorrected. Infrared spectra were measured with a Perkin-Elmer 283 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a Perkin-Elmer R32 instrument (90 MHz) and a Varian FT-80A spectrometer (20 MHz), respectively. The MS spectrum of compound **10** was obtained by a VG 70-70 EQ instrument. Silica gel plates (Merck F_{254}) and silica gel 60 (Merck, 230–400 mesh) were used for TLC, and flash chromatography, respectively. Al_2O_3 refers to the type Merck 60.

5-Benzoyl-4-nitro-3-phenylisoxazole (3):
Benzoylformyl chloride[7] (1.685 g, 10 mmol) is added to a solution of α-nitroacetophenone oxime (**1**;[8] 1.8 g, 10 mmol) in dry ether (20 mL), and the mixture is stirred at room temperature for 16 h. Removal of the solvent and HCl under reduced pressure leaves an oily residue, which is dissolved in ether (20 mL) and neutralized quickly with $NaHCO_3$ solution (10 mL). The ether phase is separated, dried (Na_2SO_4), and evaporated to dryness to give a pale yellow oil (3.0 g), largely containing the acyl oxime **2** (ca. 80%, ^{1}H-NMR) together with minor amounts of the corresponding diastereoisomer and the starting compound **1**. The crude product[9] is vigorously stirred with Al_2O_3 (6.0 g) in CH_2Cl_2 (30 mL) at room temperature for 60 h, the inorganic material is filtered off, and washed exhaustively with CH_2Cl_2 (5 × 20 mL). Evaporation of the combined filtrates to dryness affords a yellow solid (2.33 g) consisting almost exclusively (TLC, ^{1}H- and ^{13}C-NMR) of the nitroderivative **3**, which is obtained as a pure white product by flash chromatography with ether/petroleum ether 30–50 °C, (1:7) as eluent; yield: 2.06 g (70% from **1**); silky needles; mp 71 °C (*n*-hexane).

Reaction of Nitroketone 3 with Equimolar Amount of Diazomethane; Preparation of 1-Benzoyl-5-nitro-4-phenyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (5) and 6-Benzoyl-3-phenyl-5*H*-pyrazolo[3,4-*d*]isoxazole (9):
A solution of diazomethane (0.084 g, 2.0 mmol) in ether (4.2 mL) is added to compound **3** (0.589 g, 2.0 mmol) in ether (20 mL), and the mixture is set aside overnight at room temperature. By prolonged cooling of the resulting solution at −15 °C, **5** separates as a crystalline solid, which is collected by filtration (0.2 g). Evaporation to dryness of the ethereal filtrate gives an orange residue, which is resolved into three components by flash chromatography, using EtOAc/petroleum ether 40–70 °C (1:5) as eluent. The first band is identified as the unreacted compound **3** (0.14 g), the second one affords product **5** (0.014 g); total yield: 0.214 g (45%, based on recovered **3**); white needles; mp 106–106.5 °C dec (ether). Finally, the slowest running band gives **9** as a white solid; yield: 0.208 g (47%, based on recovered **3**); mp 187–188 °C dec (acetone).

Reaction of Nitroketone with an Excess of Diazomethane; Preparation of 6-Benzoyl-5-methyl-3-phenyl-5*H*-pyrazolo[3,4-*d*]isoxazole (10):
A solution of compound **3** (0.294 g, 1.0 mmol) in ether (20 mL) is treated with an excess of diazomethane (0.126 g, 3.0 mmol) in ether (6.3 mL) under the conditions described above. Removal of the solvent gives a gummy orange residue, which is resolved into two components by flash chromatography with toluene as eluent. The first band affords the cyclopropane derivative **5**; yield: 0.035 g (11%); whereas the second one is identified as **10**; yield: 0.16 g (53%); white needles; mp 162 °C (ether).

Methylation of Compound 9 to 10:
A mixture of **9** (0.1 g, 0.346 mmol) and diazomethane (0.036 g, 0.865 mmol) in ether (20 mL) is allowed to stand overnight at room temperature. Removal of solvent affords the *N*-methylderivative **10**, identical (IR and ^{1}H-NMR) with the material obtained as above; yield: 0.104 g (quantitative).

Received: 13 April 1988; revised: 14 July 1988

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(3) Elguero, J., in: *Comprehensive Heterocyclic Chemistry*, Vol. 5, Part 4A, Potts, K.T. (ed.), Pergamon Press, Oxford, 1984, p. 249.
(4) The X-ray analysis was carried out on compound **9** rather than on the corresponding *N*-methylderivative **10**, due to the difficulty of obtaining suitable crystals for the latter. Crystallographic data were deposited at Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1 EW, England, and are available from there. Tables of atomic parameters, bond geometry, and structure factors are available on request from the authors.
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(9) Attempts to obtain the acyl oxime **2** as a pure product, failed.