Unusual product from the reaction of 2-diazo-1-[5-(4-methoxybenzoyl)-2,3-dihydropyrrolizin-1-yl]ethanone with rhodium (II) acetate

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The rhodium(II)-catalysed reaction of the diazoketone derived from 5-(4-methoxybenzoyl)-2,3-dihydropyrrolizin-1-carboxylic acid (anirolac) did not give the expected intramolecular cyclisation product but afforded the 2,3-dihydropyrrolizin-1-one only an elimination product. X-ray studies confirmed the structure.

Keywords: anirolac [5-(4-methoxybenzoyl)-2,3-dihydropyrrolizin-1-carboxylic acid], pyrrole, diazoketone, rhodium (II) acetate, carbenoid

The intermolecular reactions of carbenes with electron-rich pyrroles are well known processes, with applications in the C-alkylation of pyrroles for the synthesis of hygrine derivatives.[1] Similar intramolecular carbenoid insertions at C-2 of pyrroles have been described in the literature, and these reactions have been used in the synthesis of some indolizine-based natural products.[2] In contrast, the insertion of carbenoids into the C-3H bond of pyrroles has rarely been documented.[3]

In connection with other synthetic investigations, some time ago we initiated studies on the insertion of α-ketocarbenoids into the C-3H bond of pyrroles and we have described the efficient conversion of 2-pyrrolyl-α-diazo-β-ketoesters and α-diazoketones into the corresponding bicyclic 5 and 6-membered ketones.[4]

As a continuation of these studies, we attempted to extend this methodology to pyrrolizine rings. We believed that carbenoid insertions on pyrrolizines could be used for the synthesis of strained azatriquinanes[5] which are closely related to the fenestranes.[6] A potentially good starting material to achieve this purpose is 5-(4-methoxybenzoyl)-2,3-dihydropyrrolizin-1-carboxylic acid (anirolac) (1), a member of the ketorolac group of analgesics, the synthesis of which has been described previously.[7] We found an alternative collateral reaction which did not have a precedent in the pyrrole series and which occurs instead of the carbenoid insertion. The results in this area are now reported.

We have prepared the diazoketone 2, derived from anirolac 1 (Scheme 1). The carboxylic acid 1 did not give the desired diazoketone using the coventional preparative method through the acid chloride[8] or the mixed carbonic–carboxylic anhydride.[2e] Therefore, we used another method developed by our group.[9] Treatment of anirolac 1 with an equimolar amount of triphenylphosphine, a slight excess of NBS (1.2 equiv) and followed by excess ethereal diazomethane gave the diazoketone 2 in 48% yield.

Exposure of diazoketone 2 to catalytic amounts of rhodium (II) acetate in dichloromethane solution at room temperatures afforded the bicyclic compound 3 in 45% yield (Scheme 2).

Compounds 1, 2 and 3 were characterised by conventional spectroscopic techniques. Since the bicylcic compound 3 was a crystalline solid, it was studied by X-ray crystallography. The structure of this compound is shown in Fig. 1 and some important crystallographic data are given in Tables 1 and 2.

The X-ray study revealed some interesting features of compound 3. First, the study confirmed that the product structure which lost a two-carbon chain compared to the original diazoketone 2; this agrees with prior NMR and MS analyses, specially NMR and MS. In addition, an almost planar bicyclic system of pyrrolizine is observed, where the positions 2- and 5- of pyrrole moiety are substituted by carbonyl groups, unlike molecule 2 which is substitued at C-2 by an alkyl group.

To the best of our knowledge, this is the first example of a carbenoid extrusion from a pyrrole moiety. Although the reaction mechanism is not clear, presumably this proceeds *via* a carbenoid rearrangement[10] and subsequent *ipso* substitution at C-2 in the pyrrole ring.[2e] Note that this kind of carbenoid rearrangements occurs only in pyrroles with electron withdrawing groups, whereas electron-rich pyrroles give carbenoid insertion products. On the other hand, It is

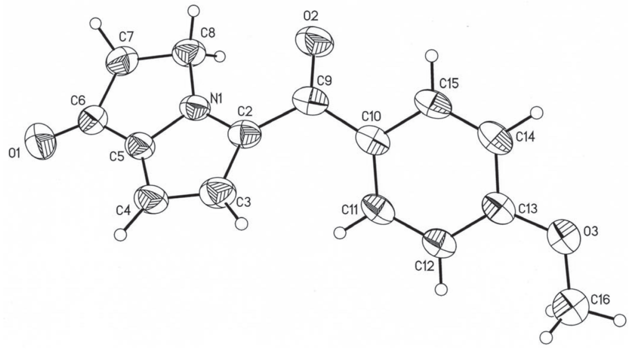
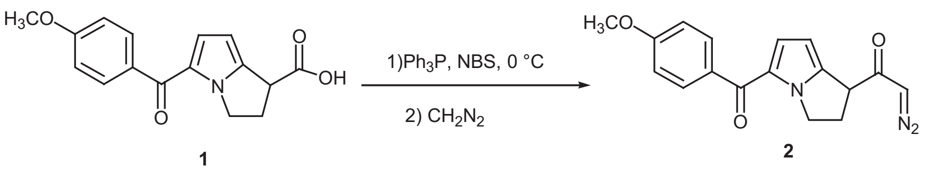


Fig. 1



Scheme 1

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Table 1 Crystal data for compound **3**

Crystal data	
Empirical formula	$C_{15}H_{13}NO_3$
Formula weight	255.26
Crystal colour	Colourless needle
Crystal system	Orthorhombic
Space group	Pbca
a	11.323(1) $\alpha = 90°$
b	7.8966(7) $\beta = 90°$
c,	27.733(2) $\gamma = 90°$
Volume, cm^3	2479.6(4)
Z	8
Density (calcd.),g/cm^3	1.368
Absorption coefficient, (mm^{-1})	0.096
F(000)	1072
Crystal size (mm)	0.42 × 0.10 × 0.08
Data collection	
Temperature, K	291(2)
Radiation, λ (Å)	0.71073
θ min, max,°	2.32,24.99
Index ranges	$-13<h<13$, $-9<k<9$, $-32<l<32$
Reflections collected	18758
Independent reflections	2187(R_{int} = 0.0611)
Observed reflects [$I>2.0\sigma(1)$]	R1 = 0.0589,wR2 = 0.1199
Refinement	
Data-to-parameter ratio	2187/0/173
R, wR2	R_1 = 0.0937,wR_2 = 0.1345
G.O.F.	1.001
Largest diff. peak, hole,e^{-3}	0.160,–0.163

Table 2 Selected bond distances (Å) and angles (°) for compound **3**

Bond	*Distance (Å)*
N(1)–C(2)	1.359(3)
C(2)–C(3)	1.397(3)
C(3)–C(4)	1.381(4)
C(4)–C(5)	1.378(3)
N(1)–C(5)	1.357(3)
C(5)–C(6)	1.445(4)
C(6)–C(7)	1.513(4)
O(1)–C(6)	1.215(3)
C(7)–C(8)	1.527(3)
N(1)–C(8)	1.469(3)
C(2)–C(9)	1.468(4)
C(9)–C(10)	1.487(3)
O(2)–C(9)	1.228(3)
C(10)–C(11)	1.386(3)
Bond	*Angle (°)*
N(1)–C(2)–C(3)	106.3(2)
N(1)–C(2)–C(9)	120.9(2)
C(4)–C(3)–C(2)	108.5(2)
C(5)–N(1)–C(2)	109.9(2)
C(5)–C(4)–C(3)	106.8(2)
N(1)–C(5)–C(6)	116.4(6)
N(1)–C(5)–C(4)	109.3(2)
C(5)–C(6)–C(7)	106.8(2)
C(6)–C(7)–C(8)	106.9(2)
N(1)–C(8)–C(7)	102.52(19)
O(1)–C(6)–C(5)	128.0(3)
O(1)–C(6)–C(7)	125.1(3)
C(5)–N(1)–C(8)	114.4(2)
C(3)–C(2)–C(9)	132.7(2)

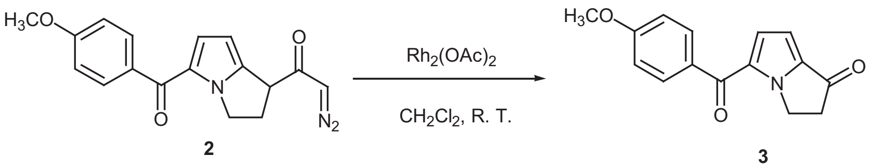
possible that the product arises by auto-oxidation of the initial diazocompound.[11] The fission of a C–C bond with the formation of a carbonyl group suggests that an oxidation is taking place.

In conclusion, this report reveals a novel reaction product which requires further experiments to elucidate the mechanistic details of the reaction.

Experimental

The starting materials were purchased from Aldrich Chemical Co. and were used without further purification. Solvents were distilled before use; ether and tetrahydrofuran (THF) were dried over sodium using benzophenone as indicator. Diazomethane was prepared from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald®) using a minimum amount of water and ethanol as a co-solvent, and dried over KOH pellets before use. Silica gel (230–400 mesh) and neutral alumina were purchased from Merck. Silica plates of 0.20-mm thickness were used for TLC. Melting points were determined with a Fisher–Johns melting point apparatus and they are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded using a Varian Gemini 200, the chemical shifts (δ) are given in ppm relative to TMS as internal standard (0.00). For analytical purposes the mass spectra were recorded on a JEOL JMS-5X 10217 in the EI mode, 70 eV, 200°C via direct inlet probe. Only the molecular and parent ions (*m/z*) are reported. IR spectra were recorded on a Nicolet Magna 55-X FT instrument. For the RX difraction studies, crystals of compound **3** were obtained by slow evaporation of a DMF solution, and the reflections were acquired with a Nicolet P3/F diffractometer. Three standard reflections every 97 reflections were used to monitor the crystal stability. The structure was solved by direct methods, missing atoms were found by difference-Fourier synthesis, and refined on F2 by a full-matrix least-squares procedure using anisotropic displacement parameters and using SHELX-97. Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre (CCDC No.668508). Copies of available materials can be obtained free of charge on application to the Director, CCDC, 12 Union Road, Cambridge CB2 IEZ, UK (fax: (44) 01223 336033); e-mail: deposit@ccdc.ac.uk.

2-Diazo–1–[5-(4–methoxybenzoyl)–2,3–dihydropyrrolizin-1-yl] ethanone (2): A precooled solution of *N*-bromosuccinimide (NBS, 0.21 g, 1.2 mmol) in THF (4 ml) in THF (5 ml) at 0°C was added dropwise to a stirred solution of triphenylphosphine (0.262 g, 1 mmol) and anirolac 1 (0.285 g, 1 mmol) under a nitrogen atmosphere. The resulting mixture was stirred at 0°C under nitrogen atmosphere for 15 min. The coolant was removed and the reaction mixture was allowed to warm to room temperature for an additional 15 min. The reaction mixture was cooled to 0°C, then an ether solution of diazomethane (5 mmol) from *N*–methyl-*N*-nitroso-4-toluenesulfonamide (1.53 g, 7.14 mmol) was added; a vigorous evolution of nitrogen occurred and the mixture was allowed to warm to room temperature overnight. The solvent was removed *in vacuo* and purification by column chromatography (SiO_2, hexane/AcOEt 7:3) afforded diazocompound 2 as yellow oil (0.15 g, 48%). IR ($CHCl_3$, cm^{-1}) 2108, 1774; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.85 (m, 2H), 3.87 (s, 3H), 3.98 (t, 1H) 4.48 (m, 2H), 5.40 (s, 1H), 6.06 (d, 1H $J_{3\text{-}4} = 3.9$ Hz), 6.83 (d, 1H, $J_{4\text{-}3} = 3.9$ Hz), 6.96 (d, 2H, $J = 8.8$ Hz), 7.85 (d, 2H, $J = 8.8$ Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 31.7, 47.4, 47.8, 54.2, 55.3, 102.7, 113.4, 113.7, 124.0, 127.4, 131.0, 131.3, 131.6, 142.0, 162.4, 183.8, 192.3; MS [EI$^+$] *m/z* (RI%); 309 [M] + (25), 281 [M-N2]$^+$ (10), 240 [M- $COCHN_2$]$^+$ (100), 135 [$CH_3OC_6H_4CO$]$^+$ (85); HRMS for $C_{17}H_{15}N_3O_3$ calcd. 309.1113, found 309.1011.



Scheme 2

5-(4-Methoxybenzoyl)-2,3-dihydropyrrolizin-1-one **(3):** A solution of the diazocompound **2** (0.309 g, 1 mmol) in dry CH_2Cl_2 (5 ml) was stirred with $Rh_2(OAc)_4$ (2 mg) under a nitrogen atmosphere at room temperature. After 2 h, the mixture was evaporated *in vacuo* and purified by column chromatography (SiO_2, hexane/AcOEt 8 : 2) to afford the compound **3** as white solid (0.11 g, 45%) m.p. 182°C, IR ($CHCl_3$, cm^{-1}) 1779, 1701; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.13 (t, 2H), 3.87 (s, 3H), 4.72 (t, 2H), 6.74 (d, 1H, $J_{4\text{-}3}$ = 4.4 Hz), 6.99 (d, 2H, $J_{3\text{-}4}$ = 4.4 Hz), 6.99 (d, 2H, J = 8.8 Hz), 7.87 (d, 2H, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 38.9, 44.3, 55.4, 106.4, 113.7, 113.7, 123.6, 128.7, 130.6, 131.3, 131.8, 136.6, 163.2, 184.6, 191.2; MS [EI$^+$] *m/z* (RI%), 255 [M]$^+$ (10), 135 [$CH_3OC_6H_4CO$]$^+$ (100); HRMS for $C_{15}H_{13}NO_3$ calcd. 255.0895, found 255.0898.

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