Intramolecular Cycloaddition Reactions of *in situ* Generated Azoalkenes; Synthesis of Pyrrolo[1,2-*b*]pyridazine Derivatives from α-Haloketone 4-Pentenoylhydrazones

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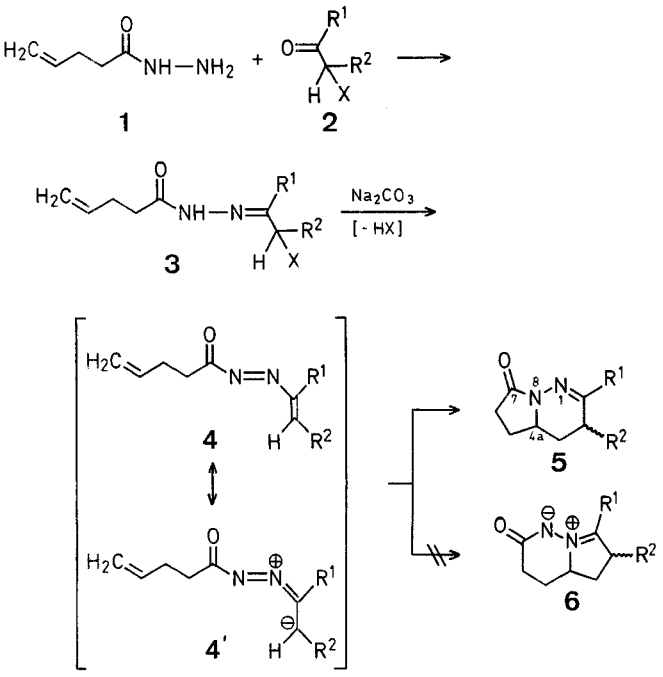
Conjugated azoalkenes have been shown to act as heterodienes in cycloaddition reactions. Two types of reaction have been distinguished: one in which an electron-deficient azoalkene adds to an electron-rich alkene, and the other in which an azoalkene bearing electron-releasing groups adds to an electron-deficient alkene[1,2]. Addition to simple unconjugated alkenes has been observed only rarely[2]. Abnormally, some azoalkenes have been shown to undergo [3+2]addition to enamines[3,4].

We have explored the possibility of carrying out intramolecular versions of these reactions. We have prepared a series of α-haloketone *N*-(4-pentenoyl)-hydrazones **(3)** from 4-pentenoic acid hydrazide **(1)** and α-haloketones **(2)**. When these hydrazones were stirred with anhydrous sodium carbonate in dichloromethane at room temperature, and the reactions monitored by ^{1}H-N.M.R. spectroscopy, the signals due to the vinyl groups gradually disappeared over periods of 12–48 h. After filtration and removal of the solvent, the intramolecular cycloadducts **5** of the *in situ* generated 1-alkenyl-(4-pentenoyl)-diazenes **4** were isolated and characterised. The products were formulated as the internal [4+2]cycloadducts **5** rather than as the isomeric [3+2]cycloadducts **6** mainly on the basis of their ^{13}C-N.M.R. spectra; in particular, they showed signals for the C-atom of the C=N group in the range $\delta = 144$–163 ppm, whereas the C-atoms of the alternative *N*-iminoiminium ylids **6** might be expected to give signals in the range 170–180 ppm[3]. The products also showed carbonyl stretching absorptions in the I.R. spectra at $\nu = 1690$–1700 cm^{-1}, typical of 5-membered lactams.



In the cases of compounds **5b**, **5c**, and **5d**, the intermediate α-chlorohydrazones **3** were not isolated and characterised, but the adducts **5** were prepared directly from the α-chloroketones **2** in a one-pot procedure.

One notable feature of the reactions is that the cycloadditions of intermediates **4** appear to be tolerant of a much wider range of substituents than the analogous intermolecular versions. None of the analogous azoalkenes, such as those derived from the corresponding α-haloketone ethoxycarbonylhydrazones, will react efficiently with simple alkenes in an intermolecular cycloaddition. The reactions, therefore, provide a good potential route to fused pyridazines with novel structures.

α-Chloroacetophenone 4-Pentenoylhydrazone (3a):

4-Pentenoic Acid Hydrazide **(1)**: A solution of ethyl 4-pentenoate (6.4 g, 50 mmol) and hydrazine hydrate (3.5 g, 70 mmol) in ethanol (100

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Table. 7-Oxo-3,4,4a,5,6,7-hexahydropyrrolo[1,2-*b*]pyridazines (**5**) prepared

5	R^1	R^2	Hal in 2 or 3	Starting Material	Reaction time [h]	Yield [%]	m.p. [°C]	Molecular formula[a]	I.R. (KBr) $\nu_{C=O}$ [cm^{-1}]	^{13}C-N.M.R. ($CDCl_3$/TMS_{int}) δ [ppm]		
										C-2	C-4a	C-7
a	C_6H_5	H	Cl	**3a**	24	80	217–218°	$C_{13}H_{14}N_2O$ (214.3)	1695	150.99	53.16	169.85
b	CH_3	H	Cl	**1** + **2b**[b]	24	23	85°	$C_8H_{12}N_2O$ (152.2)	1700	155.19	52.70	169.76
c	$-COOC_2H_5$	H	Br	**1** + **2c**[b]	24	36	137–138°	$C_{10}H_{14}N_2O_3$ (210.2)	1695	144.71	53.57	170.9
d	$-(CH_2)_4-$		Cl	**1** + **2d**[b]	48	33	114–115°	$C_{11}H_{16}N_2O$ (192.3)	1695	163.06	49.82	169.73
e	CH_3	$-COOC_2H_5$	Cl	**3e**	24	78	oil[c]	$C_{11}H_{16}N_2O_3$ (224.3)	1690[d]	148.11	49.69	169.86

[a] The microanalyses showed the following maximum deviations from the calculated values: C, ±0.36; H, ±0.06; N, ±0.12.

[b] The intermediate compounds **3** were not isolated.

[c] Characterised by hydrolysis and decarboxylation to give compound **5b**.

[d] Liquid film.

ml) is kept under nitrogen at 20 °C for 24 h. The solvent is then distilled off and the residual crude product **1** crystallised; yield: 3.2 g (56%); m.p. 45 °C (dichloromethane/hexane).

$C_5H_{10}N_2O$	calc.	C 52.61	H 8.83	N 24.54
(114.1)	found	52.60	8.86	24.65

α-Chloroacetophenone 4-Pentenoylhydrazone (**3a**): A solution of hydrazide **1** (0.27 g, 2.4 mmol) and α-chloroacetophenone (**2a**; 0.35 g, 2.3 mmol) in ethanol (6 ml) containing 2 drops of concentrated hydrochloric acid is left at room temperature for 45 min. The mixture solidifies. More ethanol (2 ml) is added and the mixture is left for a further 1 h. The crude product **3a** is isolated by suction and recrystallised from ethanol; yield: 0.50 g (85%); m.p. 124 °C.

$C_{13}H_{15}ClN_2O$	calc.	C 62.26	H 6.03	N 11.17
(250.7)	found	61.98	6.19	11.00

I.R. (Nujol): ν = 1670 cm^{-1} (C=O).

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 2.40–2.52 (m, 2H); 2.89 (t, 2H, J = 7 Hz, CH_2—CO); 4.54 (s, 2H, CH_2—Cl); 4.95–5.15 (m, 2H, H_2C=CH—); 5.8–6.0 (m, 1H, H_2C=CH—); 7.35–7.50 (m, 3H); 7.70–7.85 (m, 2H); 10.19 ppm (s, 1H, CO—NH).

Ethyl 2-Chloro-3-(4-pentenoylhydrazono)-butanoate (3e):
Prepared in the same manner as **3a**; yield: 53%; m.p. 60 °C (pentane).

$C_{11}H_{17}ClN_2O_3$	calc.	C 50.67	H 6.75	N 10.74
(260.7)	found	50.75	6.80	10.91

7-Oxo-2-phenyl-3,4,4a,5,6,7-hexahydropyrrolo[1,2-*b*]pyridazine (5a) from 3a; Typical Procedure:
Anhydrous sodium carbonate (0.15 g, 1.4 mmol) is added to a solution of α-chloroacetophenone 4-pentenoylhydrazone (**3a**; 0.10 g, 0.40 mmol) in dichloromethane (25 ml) and the mixture is stirred at room temperature for 24 h (the ^{1}H-N.M.R. signals of the vinyl group have then disappeared). The mixture is filtered through Celite® and the solvent evaporated. The residual crude product **5a** is recrystallised from dichloromethane/ether; yield: 69 mg (80%); m.p. 217–218 °C.

7-Oxo-3,4,4a,5,6,7-hexahydropyrrolo[1,2-*b*]pyridazines (5) directly from 4-Pentenoic Acid Hydrazide (1) and 1-Haloalkyl Ketones (2); General Procedure:
4-Pentenoic acid hydrazide (**1**; 571 mg, 5 mmol) and the 1-haloalkyl ketone (**2**; 5 mmol) are stirred in ether (10 ml) for 2 h. The solvent is then removed and the residue is redissolved in dichloromethane (150 ml). Sodium carbonate (1.06 g, 10 mmol) is added and the mixture is stirred for 24–48 h (until the ^{1}H-N.M.R. signals of the vinyl group have disappeared). The mixture is filtered through Celite®, the solvent removed from the filtrate, and the residual product **5** crystallised from tetrahydrofuran.

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