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Unusual reaction of *N*-aroyldihydrocyclopenta-pyrazolidinol with ketenes: formation of 1,3,4-oxadiazoles

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Abstract—1-Benzoyl-5-hydroxy-pyrazoline **1** was prepared and its reactions with ketenes, prepared in situ from the corresponding acid chlorides **3a**–**3d** and the mixed anhydride **4**, were studied. In all cases the 1,3,4-oxadiazoles **5** were isolated. In the case of compounds **3c** and **3d** a second diastereomeric oxadiazole **6** was obtained. In the case of **3a**,**3b** and **4**, an interesting aroyl migration product **7** was isolated. Structural assignments of the derived compounds were established by analysis of their IR, MS and NMR spectra (^{1}H, ^{13}C, COSY, NOESY, HETCOR and COLOC). The proposed reaction mechanism is supported by semi-empirical (AM1) MO calculations.

1. Introduction

Pyrazoles are widely used five-membered heterocyclic compounds which have been studied extensively.[1,2] Promising pharmacological and agrochemical applications[1,2] have prompted their studies. In addition, the use of some pyrazole derivatives as ultraviolet stabilizers[3] and photosensitizers,[4] as well as analytical reagents in the complexation of transition metal ions,[5] has been described. Moreover, pyrazoles and pyrazolones fused to carbocyclic rings are of interest in the chemical and pharmaceutical industry as herbicides,[6] analgesics[7] and cytotoxic agents.[8]

These applications and our interest in the chemistry of pyrazoles[9,10] prompted us to study the reaction of cyclopentapyrazoles with ketenes, because ketenes exhibit very rich cycloaddition chemistry, due to their unique structural and electronic properties.[11]

2. Results and discussion

The fused cyclopentapyrazolidinol **1** was synthesized (Scheme 1) by condensation of 2-acetylcyclopentanone with benzohydrazide in 76% yield.[12] All attempts to protect the hydroxyl group of **1** either by alkylation or acetylation failed, due to the formation of the favored aromatic pyrazole derivative **2**. Therefore, the reaction of **1** with excess of ketenes (generated in situ by the dehydrochlorination of the corresponding acid chlorides **3a**–**3d** using triethylamine) in refluxing benzene was undertaken. Compound **1** was reacted with dimethylketene to provide four products (Table 1), namely the 1-benzoylcyclopentapyrazole **2**, the 1,3,4-oxadiazole **5a**, the aroyl migration product **7a**, and a 3:1 mixture of the regioisomeric *N*-aroylsubstitution derivatives **8a1** and **8a2**. From the reaction of **1** with diphenylketene compound **2** along with the oxadiazole **5b** and the aroyl migration derivative **7b** were isolated, whereas in the case of dichloro- and chloroketene the dehydration product **2** and the 1,3,4-oxadiazoles **5c** and **5d**, respectively, were accompanied by a second diastereomeric oxadiazole derivative **6c** and **6d**. In addition, from the reaction of the more reactive dichloroketene the pyrazolylpropanodione derivative **9c** was obtained. In all cases an amount of polymeric material was also formed.

Furthermore, the reaction of **1** with the mixed anhydride **4** was studied. The anhydride, a synthetic equivalent of acid chlorides, was prepared from phenoxyacetic acid and *p*-toluenesulphonyl chloride in the presence of triethylamine in dichloromethane at room temperature. Under the mild reaction conditions employed, compound **5e** was isolated in 20% yield, along with a 3:2 regioisomeric mixture of compounds **8e1** and **8e2** (24% yield). The aroyl migration product **7e** was formed as a minor product (ca. 3% yield) detectable only by its ^{1}H NMR by comparison with the ones of **7a** and **7b**.

Finally, the reaction of **2** with dimethylketene was studied, in order to support the proposed mechanism (Scheme 3) for the formation of compounds **8** and **9**. The expected pyrazolylpropanodione derivative **9a** and the regioisomeric

Keywords: ketenes; pyrazole derivatives; regioisomeric mixture.

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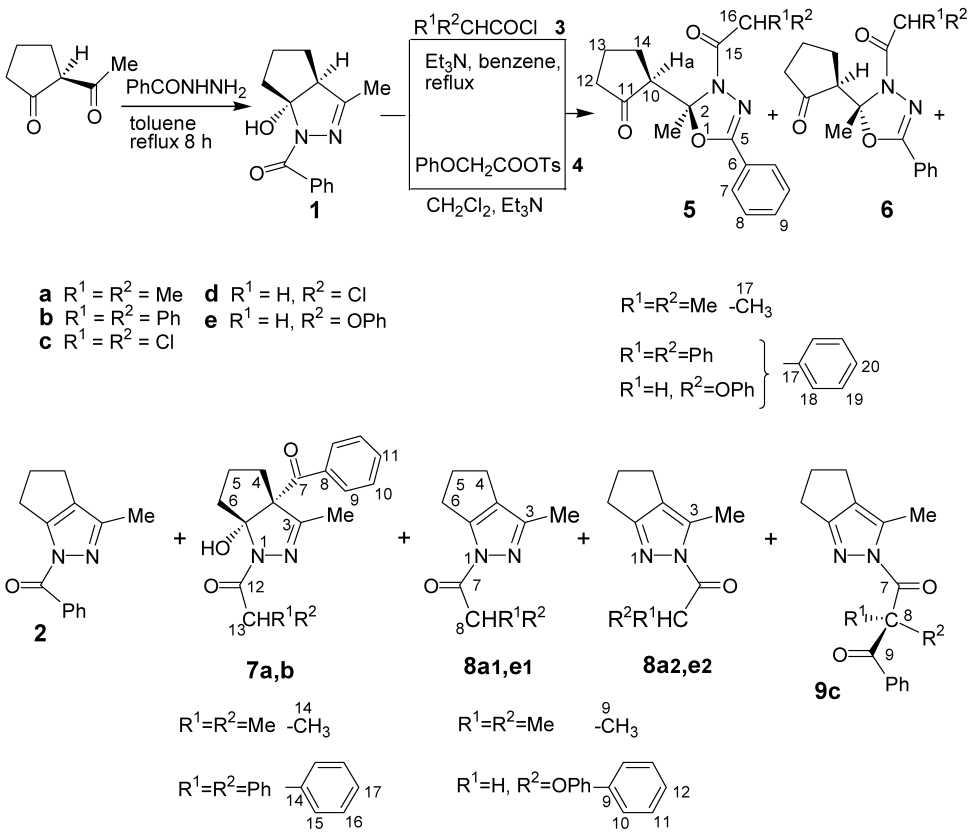


Scheme 1. Reaction of cyclopentapyrazolidinol **1** with ketenes.

mixture of **8a1**–**8a2** were formed in 30 and 9% yield, respectively.

2.1. Structure assignments

The assigned molecular structures of all new compounds **5**–**9** are based on rigorous spectroscopic analysis including IR, NMR (^{1}H, ^{13}C, COSY, NOESY, HETCOR and COLOC), MS and elemental analysis data.

Regarding the structure of oxadiazoles **5** the assignment of **5b** is described. From the molecular ion at *m*/*z* 438 the conclusion could be drawn that **5b** is produced from the reaction of one molecule of **1** with one molecule of diphenylketene, a fact that was also confirmed from the ^{13}C NMR spectrum, where 22 different signals were observed. The IR absorption at 1730 cm^{-1} and the ^{13}C NMR resonance at 215.01 ppm were consistent with the existence of a ketone carbonyl.

Furthermore, from the C–H correlated spectra in the saturated region, the presence of three methylene groups with their carbons resonating at 19.67, 25.00 and 40.07 ppm, of a methyl group at 22.24 ppm and of two methine groups at 53.96 and 54.51 ppm was established (Tables 2 and 3). By combining these data with the COSY ^{1}H–^{1}H correlations observed in the saturated region, the presence of group (**A**) was confirmed (Fig. 1) with the carbon at 40.07 ppm being next to the carbonyl.

In addition, from the COLOC correlations between the carbonyl at 215.01 ppm with the protons at δ 2.25–2.40 and 1.90–2.02, it was deduced that the last proton has a pseudo-equatorial configuration, whereas from the COLOC correlations of the methyl protons with carbons at 101.82 (^2J) and 53.96 ppm (^3J) the molecular fragment (**B**) could be extracted. Moreover, the presence of the cyclopentanone ring (*m*/*z* 83) was confirmed from the mass spectrum, where the molecular fragment at *m*/*z* 355 $[M-83]^+$ was observed. The same ion $[M-83]^+$ was also present in the mass spectra of all oxadiazole derivatives **5** and **6**.

In the aromatic region, the two protons showing a multiplet at δ 7.74–7.79 belong to C-7 being the most deshielded protons of the molecule. These protons show COLOC correlations with the quaternary carbon at 154.29 ppm and the methine carbon at 131.61 ppm across ^3J bond connectivities. In addition, the protons at δ 7.40–7.45 correlate (^3J) with the quaternary carbon at 124.41 ppm. These data indicate that the former benzoyl group of **1** has been transformed to the group (**C**). The proton at δ 5.93 correlates with an amide carbonyl at 167.96 ppm and also with the aromatic quaternary carbons at 139.25 and 139.13 ppm and with the methine carbons at 129.21 and 128.85 ppm. Therefore, it could be concluded that this group consists

Table 1. Reaction products and yields (%) of compound **1** with ketenes

R^1	R^2	**2**	**5**	**6**	**7**	**8**	**9**
Me	Me	(10)	**5a** (25)		**7a** (22)	**8a** (12)	
Ph	Ph	(14)	**5b** (20)		**7b** (28)		
Cl	Cl	(2)	**5c** (25)	**6c** (19)			**9c** (20)
Cl	H	(14)	**5d** (29)	**6d** (6)			

Table 2. ^{1}H NMR spectral data for compounds **5a–e** and **6c–d** (multiplicities and couplings in Hz)

Position	5a	5b	5c	5d	5e	6c	6d
2-Me	2.07 (s)	2.08 (s)	2.13 (s)	2.10 (s)	2.11 (s)	1.88 (s)	1.86 (s)
7	7.78–7.81 (m)	7.74–7.79 (m)	7.80–7.85 (m)	7.78–7.83 (m)	7.80–7.86 (m)	7.78–7.83 (m)	7.75–7.80 (m)
8	7.39–7.45 (m)	7.40–7.45 (m)[a]	7.42–7.50 (m)	7.42–7.48 (m)	7.42–7.49 (m)	7.40–7.47 (m)	7.38–7.45 (m)
9	7.46–7.52 (m)	7.44–7.52 (m)[a]	7.52–7.58 (m)	7.50–7.56 (m)	7.50–7.57 (m)	7.49–7.60 (m)	7.46–7.52 (m)
10a	3.45 (t, 9.2)	3.43 (t, 9.2)	3.45 (dd, 8.9, 9.8)	3.43 (dd, 8.4, 10.0)	3.43 (t, 9.2)	3.43 (dd, 8.9, 10.6)	3.48 (dd, 8.3, 9.3)
12[b]	2.32–2.43 (m)	2.25–2.40 (m)	2.32–2.46 (m)	2.34–2.46 (m)	2.34–2.45 (m)[a]	2.01–2.20 (m)[a]	2.02–2.19 (m)[a]
12	2.15–2.25 (m)	2.05–2.21 (m)	2.10–2.26 (m)	2.09–2.27 (m)	2.10–2.26 (m)	2.24–2.42 (m)	2.22–2.35 (m)
13	1.63–1.80 (m)[a]	1.59–1.70 (m)[a]	1.69–1.82 (m)	1.70–1.86 (m)	1.66–1.79 (m)	1.70–1.87 (m)	1.65–1.84 (m)
13	1.87–1.98 (m)	1.78–1.91 (m)	1.88–2.02 (m)[a]	1.88–2.04 (m)[a]	1.88–2.01 (m)	2.00–2.17 (m)[a]	2.00–2.13 (m)[a]
14	2.06–2.15 (m)[a]	1.90–2.02 (m)[a]	2.10–2.26 (m)	2.12–2.22 (m)	2.10–2.26 (m)	1.95–2.12 (m)[a]	1.98–2.12 (m)[a]
14	1.73–1.86 (m)	1.58–1.72 (m)	1.69–1.82 (m)[a]	1.72–1.82 (m)[a]	1.75–1.87 (m)[a]	2.28–2.47 (m)	2.30–2.46 (m)
16	3.32 (sep, 6.9)	5.93 (s)	6.85 (s)	4.39, 4.50 (AB, 13.7)	5.01, 5.04 (AB, 16.0)	6.92 (s)	4.53, 4.62 (AB, 14.4)
17 Me	1.19 (d, 6.9), 1.20 (d, 6.9)						
18		7.37–7.42 (m)[a,c]			6.96–7.04 (m)[a]		
19c		7.29–7.37 (m)[c]			7.27–7.35 (m)		
20c		7.21–7.28 (m)[c]			6.96–7.04 (m)[a]		

[a] Superimposed multiplets distinguished by homo- and hetero-COSY.
[b] Presented in α,β order.
[c] Values for both phenyl rings.

the former diphenylketene moiety connected to nitrogen (**D**). Finally, the chemical shift at 101.82 ppm for the quaternary carbon of fragment (**B**) suggests that this carbon most probably is connected both to nitrogen and oxygen by analogy with the C-6a carbon of structure **1**, which resonates at 103.04 ppm.[13] By combination of all the above data the oxadiazole structure **5b** can be proposed.

Concerning compounds **6c** and **6d**, they have been characterized as regioisomeric to **5c** and **5d**, respectively, on account of their very similar spectral and analytical data. The configuration on C-2 of the oxadiazoline ring has been deduced from the NOESY data of compounds **5c–5d** and **6c–6d**, where correlation spots between methyl protons and H-10a are present only in compounds **5** (see Section 2.2).

Concerning compound **7b** the molecular ion at *m/z* 438 indicated that, this derivative was also produced by reaction of one molecule of **1** with one molecule of diphenylketene without any loss. However, in this case the hydroxyl group of **1** remained unaffected and its presence was unambiguously confirmed in the IR (3400 cm^{-1}) and in the ^{1}H NMR (δ 5.03) spectra. Moreover, from the similar NMR chemical shifts of **7b** to those of the starting material[13] **1** it could be assumed that the fused cyclopentapyrazolidinol system remained unaffected. In the saturated region of the ^{13}C NMR spectrum one methyl carbon at 14.00 ppm, three methylene carbons at 23.01, 33.44 and 41.88 ppm, a methine carbon at 54.59 ppm and two quaternary carbons at 75.87 and 104.18 ppm were observed (Table 4).

In addition, the carbonyl carbons at 194.54 and 170.87 in conjunction with their IR absorptions at 1680 and 1635 cm^{-1} could be attributed to a benzoyl and an amide carbonyl, respectively. The methyl protons give COLOC correlations with the quaternary carbons at 158.48 and 75.87 ppm, whereas the hydroxyl hydrogen correlates with the same quaternary carbon at 75.87 ppm and also with the quaternary carbon at 104.18 ppm. From these data the signal at 75.87 ppm could be assigned to C-3a, the signal at 158.48 ppm to C-3 and the signal at 104.18 ppm to the hydroxylated carbon C-6a. From the ^{1}H–^{1}H and ^{13}C–^{1}H COSY of the aromatic region the benzoyl group could be assigned. The multiplet at δ 7.53–7.62 belongs to the protons of C-9 and correlates with the carbonyl carbon at 194.54 ppm but also with the methine carbon at 132.62 ppm. In addition, the proton at δ 5.99 correlates with the amide carbonyl at 170.87 ppm, with the aromatic quaternary carbons at 139.14 and 139.06 ppm but also with the methine carbons at 129.14 and 128.94 ppm. These data indicate that this group consists the former diphenylketene moiety connected to N-1. The absence of the bridge H-3a in connection with the substantial chemical shift change of C-3a and H-4a compared to the parent compound **1**, from 59.67 to 75.87 ppm, and from δ 2.11 to 2.977, respectively, shows the position of the benzoyl attachment.

The PhCO-3a and HO-6a substituents offer an additional rigidity to the fused molecule, so that the combined influence of all substituents on the chemical shifts of the cyclopentane-ring methylene protons results to well resolved individual multiplets for each proton. From the ^{1}H–^{1}H and ^{13}C–^{1}H COSY of the aliphatic region the

Table 3. ^{13}C NMR data for compounds **5a**–**5e** and **6c**–**6d**

Position	5a	5b	5c	5d	5e	6c	6d
2	101.53	101.82	102.28	102.00	101.97	101.55	101.32
2-Me	22.53	22.24	22.07	22.29	22.43	22.81	23.46
5	154.17	154.29	156.09	155.40	155.42	155.36	154.57
6	124.71	124.41	123.52	123.91	124.06	123.85	124.26
7	126.80	126.85	127.24	127.03	127.00	127.14	126.90
8	128.68	128.65	128.86	128.78	128.78	128.70	128.64
9	131.49	131.61	132.41	132.03	131.97	132.10	131.72
10	53.43	53.96	53.47	53.66	53.89	51.11	50.71
11	215.18	215.01	214.24	210.65	214.61	213.16	213.70
12	40.18	40.07	39.92	40.00	40.03	38.96	39.14
13	19.73	19.67	19.63	19.66	19.67	19.89	19.93
14	25.23	25.00	24.91	25.12	25.30	25.94	25.98
15	173.52	167.96	158.94	162.04	163.85	159.57	162.86
16	54.06	54.51	64.38	42.00	65.61	64.42	42.57
17	18.79, 18.37	139.25,[a] 139.13[a]			158.21		
18		129.21,[b] 128.85[b]			114.73		
19		128.51,[c] 128.43[c]			129.53		
20		127.05,[d] 126.97[d]			121.51		

[a,b,c,d]Values are interchangeable between the two phenyls.

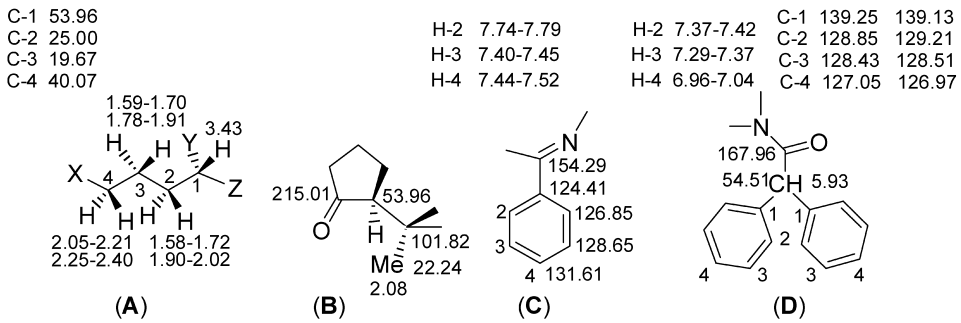


Figure 1. Molecular fragments extracted from the compilation of spectral data of **5b**.

sequence for the three CH_2 groups of cyclopentane could be assigned. To determine the exact values of chemical shifts and coupling constants of these protons the corresponding part of ^{1}H NMR spectra of both compounds **7a** and **7b** was reproduced by simulation (Table 5). On the basis of our previous work[13] on compound **1** and in conjunction with molecular modeling on compounds **7** (AM1), it was concluded that the conformation of the cyclopentane ring is similar to the one of **1**. From the model of **7a** depicted in Figure 2 the torsion angles between the methylene protons and the carbons C-3a and C-6a, being three bonds away, could be extracted. These angles for the protons H-4b, H-5a and H-6b vary from 132 to 146° and for the protons H-4a, H-5b and H-6a from 95 to 109°. The COSY correlation between H-4b and H-6b (^4J=1.7 Hz) is in accordance with the proposed 'W' configuration resulted from a pseudo-equatorial conformation of protons H-4b, H-5a and H-6b. This configuration is also supported by the COLOC correlations between the protons H-4b at 1.723 and H-5a at 1.897 with carbon C-6a and between the protons H-5a and H-6b (at 2.743) with carbon C-3a via ^3J(C–H). On the other hand, the chemical shift difference between the protons at the same methylene carbon ($\Delta\delta_{C\text{-}4}$=1.223, $\Delta\delta_{C\text{-}5}$=0.478, $\Delta\delta_{C\text{-}6}$=0.510) can be explained by the downfield influence of the benzoyl group at C-3a on proton H-4a and of the amide carbonyl on H-6b, and by the upfield influence of N=C bond on H-5b.

Compounds **8** were assigned utilizing their similarity[12] with compounds **2a**,**b** (Table 6).

Finally, concerning compound **9c** it was confirmed that the carbonyl substituent was on N-2 on account of its spectroscopic data (Table 7). Analytically, the methyl protons show COLOC correlations with the quaternary carbons resonating at 130.10 and 136.67 ppm, whereas the methylene protons at δ 2.46 correlate with the quaternary carbon at 167.41 ppm. This signal is attributed to the C-6a forming a double bond with N-1, whereas the amide carbonyl carbon resonates at 161.86 ppm. Analogous chemical shift for C-6a was observed in the case of **9a**.

It is worth mentioning that from our studies on fused pyrazole derivatives the conclusion can be drawn that the value for the chemical shift of C-6a ranging from ca. 160–168 ppm can be used as a diagnostic tool for the identification of N-2 substituted pyrazole derivatives, whereas in the analogous N-1 substituted pyrazole derivatives the corresponding value is ranging ca.150–155 ppm.

2.2. Reaction mechanisms

From the isolation of products **5**–**7** on one hand and **8** and **9** on the other hand the reaction mechanisms depicted in Schemes 2 and 3 can be proposed. As shown in Scheme 2,

Table 4. ^{13}C, ^{1}H and COLOC NMR data for compounds **7a** and **7b**

Position	Compound **7a**			Compound **7b**		
	C	H[a]	COLOC[b]	C	H[a]	COLOC[b]
3	157.87			158.48		
3-Me	13.97	1.69 (s)	157.85, 75.89	14.00	1.62 (s)	158.48, 75.87
3a	75.90			75.87		
4	33.59	2.93–3.04 (m),[c] 1.71–1.76 (m)		33.44	2.93–3.33 (m),[c] 1.69–1.73 (m)	104.18
5	23.18	1.87–1.98 (m), 1.37–1.53 (m)		23.01	1.83–1.95 (m), 1.33–1.49 (m)	104.18, 75.87
6	41.94	2.11–2.23 (m), 2.64–2.73 (m)		41.88	2.11–2.21 (m), 2.71–2.79 (m)	23.01, 104.18, 75.87
6a	104.08			104.18		
OH		5.01 (br, s)	75.89		5.03 (s)	104.18, 75.87
7	195.16			194.54		
8	137.73			137.31		
9	128.84	7.75–7.81 (m)	195.14, 132.63	128.78[d]	7.53–7.62 (m)	194.54, 132.62
10	128.24	7.35–7.43 (m)	137.71	128.17	7.11–7.20 (m)	137.31
11	132.64	7.48–7.55 (m)		132.62	7.39–7.47 (m)	
12	176.63			170.87		
13	32.10	3.38 (sep, 6.9)		54.59	5.99 (s)	170.87, 139.14, 139.06, 129.14, 128.94
14	18.40	1.21 (d, 6.9)	176.62, 32.10, 18.75	139.14,[e] 139.06		
15	18.75	1.27 (d, 6.9)	176.62, 18.40	129.14, 128.94	7.30–7.44,[f] 7.40–7.52	
16				128.73,[d] 128.43	7.30–7.47, 7.30–7.47	
17				127.10, 127.09	7.22–7.29, 7.33–7.40	

[a] Multiplicities and couplings in Hz in parentheses. For exact values of chemical shifts and coupling constants of cyclopentane-ring protons see Table 5.
[b] Long-range ($^{2}J_{C-H}$ and $^{3}J_{C-H}$) correlations between the protons on the left and the carbons stated on the column.
[c] Presented in α,β order.
[d] May be interchanged.
[e] For both phenyls.
[f] Superimposed multiplets distinguished by homo- and hetero-COSY.

Table 5. Chemical shifts and $^{n}J_{(H,H)}$ coupling constants fitted to the best simulated spectra for the cyclopentane methylene protons of compounds **7a** and **7b**

Compound **7a**							Compound **7b**						
	H-4a	H-4b	H-5a	H-5b	H-6a	H-6b		H-4a	H-4b	H-5a	H-5b	H-6a	H-6b
	2.985	1.762	1.927	1.449	2.176	2.686		2.977	1.723	1.897	1.411	2.161	2.743
H-4a		−13.6	6.0	12.0	0.0	0.0	H-4a		−13.2	6.2	12.0	0.0	0.0
H-4b			2.5	5.5	0.0	1.7	H-4b			2.5	5.7	0.0	1.7
H-5a				−13.0	6.4	2.6	H-5a				−12.7	6.3	2.3
H-5b					12.3	6.1	H-5b					12.1	5.7
H-6a						−13.2	H-6a						−13.0

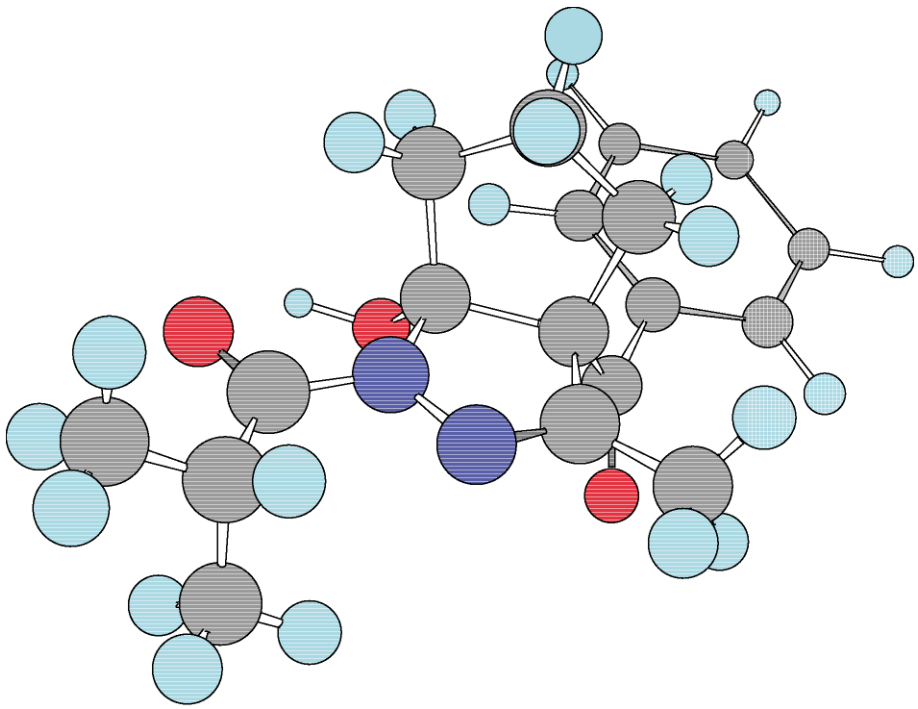


Figure 2. Molecular model of the compound **7a** (AM1).

Table 6. ^{1}H and ^{13}C NMR spectral data for the isomers **8a1**,**a2** and **8e1**,**e2** (multiplicities and *J* in Hz)

Position	**8a1**	**8a2**	**8e1**	**8e2**	**8a1**	**8a2**	**8e1**	**8e2**
3					147.81	136.00	149.13	128.42
3-Me	2.21 (s)	2.51 (s)	2.19 (s)	2.49 (s)	13.05	14.15	13.52	13.03
3a					130.85	128.81	131.37	136.12
4	2.49–2.60 (m)[a]	2.49–2.60 (m)[a]	2.44–2.58 (m)	2.32–2.43 (m)	22.14	21.85	21.74	22.09
5	2.49–2.60 (m)[a]	2.49–2.60 (m)[a]	2.44–2.58 (m)	2.32–2.43 (m)	30.33	29.55	29.63	30.31
6	2.96–3.03 (m)	2.70 (t, 7.2)	2.93–3.00 (m)	2.67 (t, 7.3)	27.17	24.53	26.62	24.32
6a					152.32	165.23	152.43	166.34
7					176.21	178.42	168.28	166.89
8	3.79 (sep, 7.0)	3.88 (sep, 7.0)			31.68	33.03	65.73	66.61
9	1.26 (d, 7.0)	1.26 (d, 7.0)	5.36 (s)	5.38 (s)	19.11	19.26	158.09	158.07
10			6.94–7.00 (m)	6.94–7.00 (m)			114.81	114.87
11			7.22–7.30 (m)	7.22–7.30 (m)			129.49	129.49
12			6.86–6.93 (m)	6.86–6.93 (m)			121.54	121.63

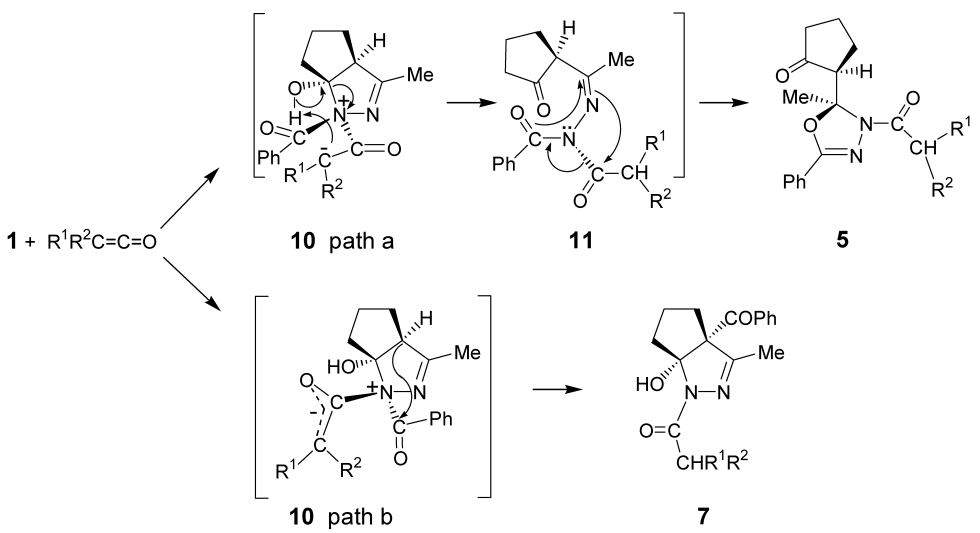
As a 3:1 mixture for compounds **8a1**,**a2** and 3:2 or compounds **8e1**,**e2**.
[a] Superimposed multiplets distinguished by homo- and hetero-COSY.

the reaction is most probably initiated by an attack of N-1 of **1** to the ketene carbonyl giving intermediate **10**. This attack is supported by semi-empirical MO calculations (AM1) on compound **1** which gave for N-1 net charge $q=-0.30$ electrons and HOMO p_z coefficient=0.62, whereas the corresponding values for N-2 are −0.001 and −0.36. When ketene approaches N-1 from the *exo* side of the fused pyrazolidine ring (path a), proton abstraction of the hydroxyl group by the ketene moiety is favorable causing subsequent fission of the pyrazolidine ring (intermediate **11**, Fig. 3). This fission is followed by attack at the former C-3 by the more electron-rich oxygen of the benzoyl group with

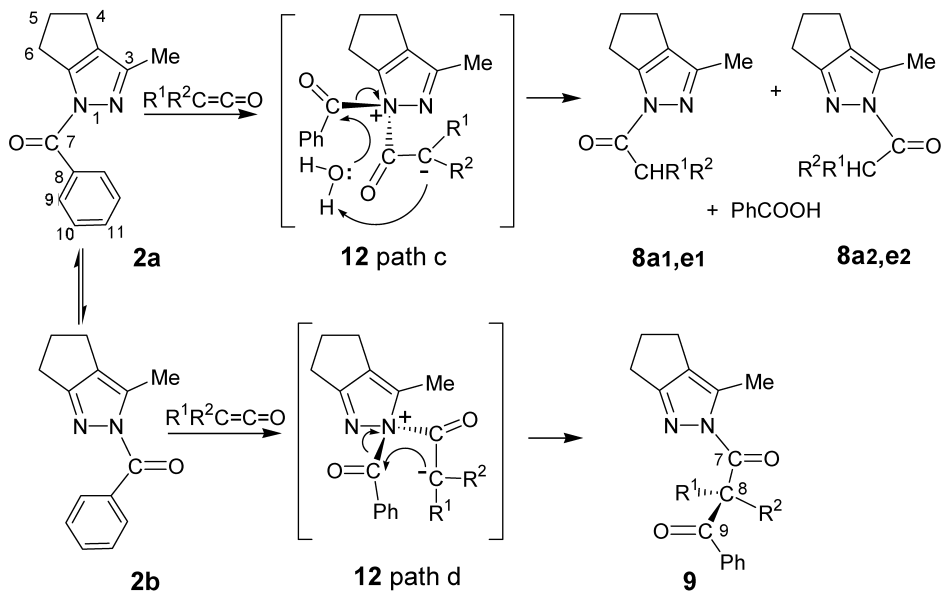
Table 7. ^{13}C, ^{1}H and COLOC NMR data for compounds **9a** and **9c**

Position	Compound **9a**			Compound **9c**		
	C	H[a]	COLOC[b]	C	H[a]	COLOC[b]
3	135.56			136.67		
3-Me	13.81	2.48 (s)	135.56, 128.78	13.28	2.50 (s)	136.67, 130.10
3a	128.78			130.10		
4	21.55	2.39[c] (t, 7.0)	165.72, 128.78, 29.22	21.60	2.44[c] (t, 7.0)	167.41, 130.10, 29.26
5	29.22	2.18 (qui, 7.0)	21.55, 24.22	29.26	2.24 (qui, 7.0)	21.60, 24.25
6	24.22	2.41[c] (t, 7.0)	165.72, 128.78	24.25	2.46[c] (t, 7.0)	167.41, 130.10
6a	165.72			167.41		
7	175.35			161.86		
8	55.23			85.50		
8-Me	24.93	1.70	175.35, 55.23			
9	196.98			182.72		
10	136.79			133.13		
11	127.80	7.76–7.81 (m)	131.54	128.97	7.87–7.91 (m)	182.72, 132.83
12	128.12	7.27–7.34 (m)	136.79	128.40	7.34–7.41 (m)	133.13
13	131.54	7.34–7.41 (m)	127.80	132.83	7.45–7.51 (m)	128.97

[a]Multiplicities and *J* in Hz in parentheses. [b]Long-range ($^{2}J_{C-H}$ and $^{3}J_{C-H}$) correlations between the protons on the left and the carbons stated on the column. [c]Superimposed multiplets distinguished by homo- and hetero-COSY.



Scheme 2. Plausible mechanism for the reaction of **1** with ketenes explaining the formation of **5**–**7**.



Scheme 3. Plausible mechanism for explaining the formation of **8** and **9**.

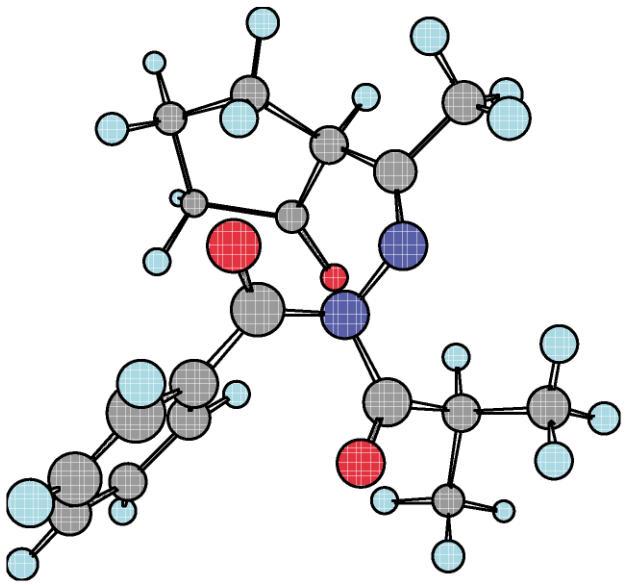


Figure 3. Molecular model of the intermediate **11** (R^1=R^2=CH_3) (AM1).

simultaneous shift of the ketene moiety. Thus, the formation of regioisomers **5** (2*S*) can be explained. To the contrary, when the ketene molecule approaches N-1 from the *endo* side (path b), proton abstraction of the hydroxyl group is less favorable and occurs only in the case of the more reactive chloro- and dichloroketenes giving the regioisomeric oxadiazoles **6** (2*R*). In the case of dimethyl-, diphenyl- and phenoxyketenes of moderate reactivity, abstraction of the hydroxyl proton is not favored and benzoyl migration at the former C-3a occurs leading to the formation of compound **7**.

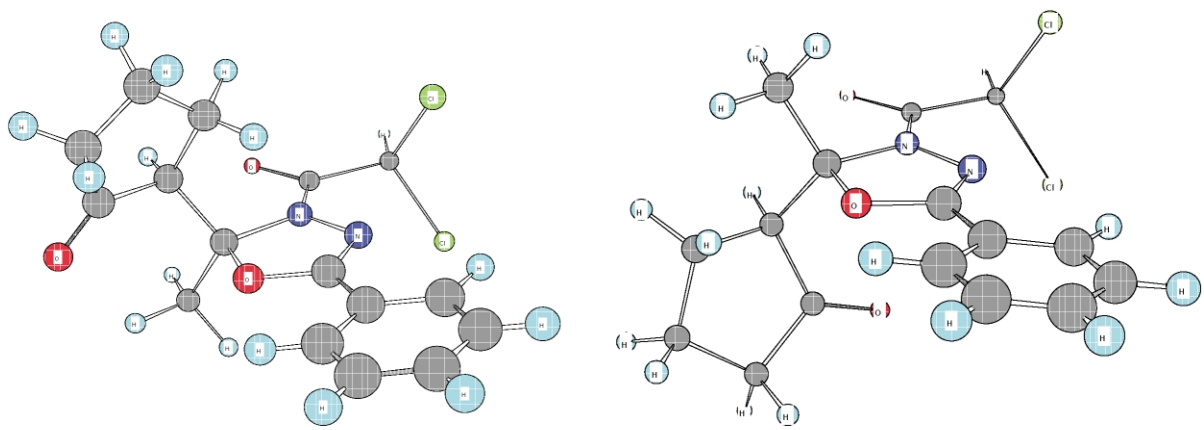
The proposed mechanisms are also supported by the yield ratio of the chloroderivatives **5c**, **6c** (25%, 19%) and **5d**, **6d** (29, 6%), where the more reactive dichloroketene gives approximately the same yields for both isomers.

In order to distinguish between the two possible regioisomers **5** and **6** MO calculations (AM1) have been carried out affording the more stable conformation of each regioisomer, depicted in Figure 4, for regioisomers **5c** and **6c**. The methyl group is more crowded in the 2*S* than in the 2*R* configuration being between the two carbonyls. In this way, the downfield shift of the methyl protons of regioisomer **5c** (δ 2.13) over the corresponding of **6c** (δ 1.88) and their ^{13}C chemical shifts 22.07 over 22.81, respectively, could be explained. In addition, the calculated dipole moment of the 2*S* isomer (3.19 D) is lower than the corresponding value (3.96 D) of the 2*R* in agreement with their column elution order and also with their mp, where the mp of **5** is lower than the one of **6** in both isolated isomeric pairs (see Section 4).

Formation of products **8** and **9** could be explained by accepting a process involving initial dehydration of **1** to **2a**. Subsequent benzoyl migration from N-1 to N-2 of **2a** can occur easily in solution yielding a 3:1 equilibrium mixture[12] of isomeric pairs **2a** and **2b**. Quaternization of the N-sp^3 by the excess of ketene yields the zwitterions **12** of both **2a** and **2b** (Scheme 3). Elimination of benzoic acid leads to compounds **8** (reaction path c), whereas intramolecular attack of the benzoyl carbonyl carbon by the carbanion of the ketene moiety gives **9** as a single substituted isomer on N-2 (reaction path d). An additional proof for the proposed mechanism is the formation of benzoic acid in the case of the reaction of **1** with **3a** and **4** and the increased yield of **2** in the case of **3b**. In order to establish the initial formation of **2** and the mechanism proposed in Scheme 3 the reaction of **2** with dimethylketene was studied, whereupon the expected pyrazolyl propanodione derivative **9a** and the regioisomeric mixture of **8a1**–**8a2** were formed in 30 and 9% yield, respectively.

3. Conclusion

In conclusion, we have studied an unusual reaction of a fused cyclopentapyrazolidinol with ketenes leading to unexpected products. The proposed mechanisms offer a rational explanation for the regioselectivity found. In addition, from the above studies on fused pyrazole derivatives the value for the chemical shift of C-6a ranging from ca. 160–168 ppm can be used as a diagnostic tool for



5c (2*S*) **6c** (2*R*)

Figure 4. Molecular models of the diastereoisomers **5c** and **6c** at their most stable conformation (AM1).

the identification of N-2 substituted pyrazole derivatives, whereas in the analogous N-1 substituted pyrazole derivatives the corresponding value is ranging ca. 150–155 ppm.

4. Experimental

4.1. General

Melting points were measured on a Kofler hot-stage and are uncorrected. Column chromatography was carried out using Merck silica gel. Petroleum ether refers to the fraction boiling between 60 and 80°C. NMR spectra were recorded on a Bruker AM 300 spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C, respectively, using $CDCl_3$ as solvent. The chemical shifts are expressed in δ values (ppm) relative to TMS as internal standard for ^{1}H and relative to TMS (0.00 ppm) or to $CDCl_3$ (77.05 ppm) for ^{13}C NMR spectra. Coupling constants ^nJ are reported in Hz. The following abbreviations are used to describe spin multiplicity: s=singlet, d=doublet, t=triplet, q=quartet, qui=quintet, sex=sextet, sep=septet, m=multiplet, br=broad, dd=double of doublets, dt=double of triplets. IR spectra were recorded on a Perkin–Elmer 297 spectrometer and are reported in wave numbers (cm^{-1}). Low-resolution electron impact mass spectra (EIMS) were obtained on a VG TS-250 instrument and elemental analyses performed with a Perkin–Elmer 2400-II CHN analyzer. The MO calculations for minimum energy conformation of compounds were computed with the AM1 method as implemented in the MOPAC package[14] version 6.3. All stationary points were refined by minimization of the gradient norm of the energy to at least 0.005 kcal/mol.

4.2. Reaction of pyrazolidinol 1 with dimethylketene—general procedure

A solution of isobutyryl chloride (**3a**) (0.21 g, 2.0 mmol) in dry benzene (5 mL) was added dropwise at room temperature for 2 h to a stirred solution of **1** (0.244 g, 1.0 mmol) and Et_3N (0.21 g, 2.1 mmol) in dry benzene (20 mL). The reaction mixture was stirred under reflux for 4 h and then a further quantity of Et_3N (2.1 mmol) was added followed by the dropwise addition of isobutyryl chloride (2.0 mmol) in dry benzene (5 mL). The reaction mixture was stirred under reflux for a further 4 h and then washed with a 10% $NaHCO_3$ aqueous solution (10 mL). The organic layer was separated, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using petroleum ether/EtOAc as eluent, slowly increasing the polarity to give in order of elution.

4.2.1. 1,4,5,6-Tetrahydro-3-methyl-1-(2-methyl-1-oxopropyl)-cyclopenta[*c*]pyrazole (8a1) and 2,4,5,6-tetrahydro-3-methyl-2-(2-methyl-1-oxopropyl)-cyclopenta[*c*]-pyrazole (8a2). As a 3:1 mixture of regioisomers (0.023 g, 12%). White solid, mp 112–115°C, R_f (petr. ether/EtOAc 10:1)=0.82. ^{1}H and ^{13}C NMR: Table 6. IR (nujol) ν_{max} 1705 cm^{-1}. EIMS *m/z* (%) 192 (9, M^+), 122 (100), 69 (52). Anal. calcd for $C_{11}H_{16}N_2O$ (192.26): C, 68.72; H, 8.39; N, 14.57. Found: C, 68.81; H, 8.34; N, 14.41.

4.2.2. 1-Benzoyl-1,4,5,6-tetrahydro-3-methyl-cyclopenta[*c*]pyrazole (2). White solid,[12] (0.023 g, 10%), mp 44–46°C, R_f=0.70.

4.2.3. (2*S*)-2,3-Dihydro-2-methyl-3-(2-methyl-1-oxopropyl)-2-(2-oxocyclopentyl)-5-phenyl-1,3,4-oxadiazole (5a). White solid (0.078 g, 25%), mp 102–103°C (EtOH), R_f=0.40. ^{1}H and ^{13}C NMR: Tables 2 and 3. IR (neat) ν_{max} 1720, 1645, 1620 cm^{-1}. EIMS *m/z* (%) 314 (12, M^+), 244 (17), 231 (14), 161 (100). Anal. calcd for $C_{18}H_{22}N_2O_3$ (314.39): C, 68.77; H, 7.05; N, 8.91. Found: C, 68.82; H, 7.00; N, 8.80.

4.2.4. 3a-Benzoyl-4,5,6,6a-tetrahydro-6a-hydroxy-3-methyl-1-(2,2-dimethylacetyl)-cyclopenta[*c*]pyrazole (7a). White solid (0.069 g, 22%), mp 138–139°C (EtOH), R_f=0.24. ^{1}H, ^{13}C and COLOC NMR: Table 4. IR (neat) ν_{max} 3360, 1675, 1635 cm^{-1}. EIMS *m/z* (%) 314 (10, M^+), 244 (14), 192 (8), 171 (62), 122 (32), 105 (100). Anal. calcd for $C_{18}H_{22}N_2O_3$ (314.39): C, 68.77; H, 7.05; N, 8.91. Found: C, 68.70; H, 7.09; N, 8.83.

4.3. Reaction of 1 with diphenylketene

The reaction was carried out as described above with 1 mmol of **1** to afford after column chromatography compound **2** (0.032 g, 14%).

4.3.1. (2*S*)-2,3-Dihydro-2-methyl-3-(2,2-diphenylacetyl)-2-(2-oxocyclopentyl)-5-phenyl-1,3,4-oxadiazole (5b). White solid (0.088 g, 20%), mp 145–146°C (Et_2O/petroleum ether). ^{1}H and ^{13}C NMR: Tables 2 and 3. IR (nujol) ν_{max} 1730, 1650, 1620 cm^{-1}. EIMS *m/z* (%) 438 (49, M^+), 355 (6), 244 (82), 194 (57), 192 (15), 168 (68), 167 (98), 166 (75), 165 (100), 162 (40), 161 (96), 152 (61), 115 (10), 105 (98). Anal. calcd for $C_{28}H_{26}N_2O_3$ (438.53): C, 76.69; H, 5.98; N, 6.39. Found: C, 76.73; H, 5.82; N, 6.36.

4.3.2. 3a-Benzoyl-4,5,6,6a-tetrahydro-6a-hydroxy-3-methyl-1-(2,2-diphenylacetyl)-cyclopenta[*c*]pyrazole (7b). White solid (0.123 g, 28%), mp 192–193°C (EtOH). ^{1}H, ^{13}C and COLOC NMR: Table 4. IR (nujol) ν_{max} 3400, 1680, 1635 cm^{-1}. EIMS *m/z* (%) 439 (38, M^+), 421 (4), 411 (5), 317 (19), 245 (37), 169 (44), 153 (95), 140 (50), 128 (59), 111 (69), 105 (65), 91 (55), 83 (100). Anal. calcd for $C_{28}H_{26}N_2O_3$ (438.53): C, 76.69; H, 5.98; N, 6.39. Found: C, 76.49; H, 5.80; N, 6.50.

4.4. Reaction of 1 with dichloroketene

The reaction was carried out as described above with 1 mmol of **1** to give in elution order after column chromatography compound **2** (0.005 g, 2%).

4.4.1. 2-(2-Benzoyl-2,2-dichloroacetyl)-2,4,5,6-tetrahydro-3-methylcyclopenta[*c*]pyrazole (9c). White solid (0.067 g, 20%), mp 155–156°C (Et_2O/petroleum ether). ^{1}H, ^{13}C and COLOC NMR: Table 7. IR (nujol) ν_{max} 1730, 1670, 1620 cm^{-1}. EIMS *m/z* (%) 336/338/340 (33, M^+), 308/310/312 (7), 226 (8), 192 (12). Anal. calcd for $C_{16}H_{14}Cl_2N_2O_2$ (337.21): C, 56.99; H, 4.18; N, 8.31. Found: C, 56.89; H, 3.99; N, 8.16.

4.4.2. (2*S*)-3-(2,2-Dichloroacetyl)-2,3-dihydro-2-methyl-2-(2-oxocyclopentyl)-5-phenyl-1,3,4-oxadiazole (5c). White solid (0.089 g, 25%), mp 97–98°C (EtOH). ^{1}H and ^{13}C NMR: Tables 2 and 3. IR (nujol) ν_{max} 1730, 1670 cm^{-1}. EIMS *m/z* (%) 354/356/358 (17, M$^+$), 271 (90), 243 (16), 229 (37) 161 (100), 105 (99). Anal. calcd for $C_{16}H_{16}Cl_2N_2O_3$ (355.22): C, 54.10; H, 4.54; N, 7.89. Found: C, 54.19; H, 4.65; N, 7.91.

4.4.3. (2*R*)-3-(2,2-Dichloroacetyl)-2,3-dihydro-2-methyl-2-(2-oxocyclopentyl)-5-phenyl-1,3,4-oxadiazole (6c). White solid (0.067 g, 19%), mp 124–125°C (EtOH). ^{1}H and ^{13}C NMR: Tables 2 and 3. IR (neat) ν_{max} 1730, 1670, 1620 cm^{-1}. EIMS *m/z* (%) 354/356/358 (60, M$^+$), 270 (77), 244 (65), 161 (79), 111 (100). Anal. calcd for $C_{16}H_{16}Cl_2N_2O_3$ (355.22): C, 54.10; H, 4.54; N, 7.89. Found: C, 54.08; H, 4.46; N, 7.71.

4.5. Reaction of 1 with chloroketene

The reaction was carried out as described above with 1 mmol of **1** to give after column chromatography compound **2** (0.032 g, 14%).

4.5.1. (2*S*)-2,3-Dihydro-2-methyl-3-(2-chloroacetyl)-2-(2-oxocyclopentyl)-5-phenyl-1,3,4-oxadiazole (5d). White solid (0.093 g, 29%), mp 96–97°C (EtOH). ^{1}H and ^{13}C NMR: Tables 2 and 3. IR (nujol) ν_{max} 1730, 1650, 1620 cm^{-1}. EIMS *m/z* (%) 320/322 (15, M$^+$), 245 (7), 237 (28), 161 (92), 105 (81), 77 (100). Anal. calcd for $C_{16}H_{17}ClN_2O_3$ (320.78): C, 59.91; H, 5.34; N, 8.73. Found: C, 59.82; H, 5.48, N, 8.57.

4.5.2. (2*R*)-2,3-Dihydro-2-methyl-3-(2-chloroacetyl)-2-(2-oxocyclopentyl)-5-phenyl-1,3,4-oxadiazole (6d). White solid (0.019 g, 6%), mp 106–108°C (EtOH). ^{1}H and ^{13}C NMR: Tables 2 and 3. EIMS *m/z* (%) 320/322 (7, M$^+$), 246 (1), 237 (10), 161 (100), 105 (65), 77 (58). Anal. calcd for $C_{16}H_{17}ClN_2O_3$ (320.78): C, 59.91; H, 5.34; N, 8.73. Found: C, 59.79; H, 5.27, N, 8.62.

4.6. Reaction of 1 with the anhydride 5 in the presence of Et_3N

A solution of phenoxyacetic acid (0.46 g, 3.0 mmol), toluene-*p*-sulphonyl chloride (0.57 g, 3.0 mmol), and Et_3N (0.61 g, 6.0 mmol) in dry CH_2Cl_2 (15 mL) was stirred at room temperature for 10 min. To this solution the pyrazolidinol **1** (0.244 g, 1.0 mmol) was added in dry CH_2Cl_2 (2 mL) and the solution was stirred at room temperature for 24 h. A further quantity of phenoxyacetic acid-toluene-*p*-sulphonyl chloride-Et_3N solution, prepared as above, was added and stirring was continued for 24 h. The reaction mixture was then washed with a 10% $NaHCO_3$ aqueous solution (10 mL), with water (20 mL) and dried. The solvent was evaporated and the residue was chromatographed on silica gel column with petroleum ether/EtOAc as eluent with slowly increasing polarity to give the following compounds in elution order.

Compound **2** (0.032 g, 14%).

4.6.1. 1,4,5,6-Tetrahydro-3-methyl-1-(2-phenoxyacetyl)-cyclopenta[*c*]pyrazole (8e1) and 2,4,5,6-tetrahydro-3-methyl-2-(2-phenoxyacetyl)-cyclopenta[*c*]pyrazole (8e2). As a 3:2 mixture (0.062 g, 24%), white solid, mp 88–90°C. ^{1}H and ^{13}C NMR: Table 6. IR (nujol) ν_{max} 1705 cm^{-1}. EIMS *m/z* (%) 256 (17, M$^+$), 135 (63), 122 (50), 91 (90), 77 (100). Anal. calcd for $C_{15}H_{16}N_2O_2$ (256.31): C, 70.29; H, 6.29; N, 10.93. Found: C, 70.35; H, 6.12; N, 10.78.

4.6.2. (2*S*)-2,3-Dihydro-2-methyl-2-(2-oxocyclopentyl)-3-(2-phenoxyacetyl)-5-phenyl-1,3,4-oxadiazole (5e). White solid (0.083 g, 22%), mp 80–81°C (EtOH). ^{1}H and ^{13}C NMR: Tables 2 and 3. IR (neat) ν_{max} 1720, 1645, 1620 cm^{-1}. EIMS *m/z* (%) 378 (5, M$^+$), 295 (7), 161 (11), 107 (66), 77 (100). Anal. calcd for $C_{22}H_{22}N_2O_4$ (378.43): C, 69.83; H, 5.86; N, 7.40. Found: C, 70.03; H, 5.80; N, 7.52.

4.7. Reaction of 2 with dimethylketene

A solution of isobutyryl chloride (**3a**) (0.21 g, 2.0 mmol) in dry C_6H_6 (5 mL) was added dropwise at room temperature for 1 h to a stirred solution of **2** (0.226 g, 1.0 mmol) and Et_3N (0.21 g, 2.1 mmol) in dry benzene (20 mL). The reaction mixture was stirred under reflux for 4 h and then the previously described work-up procedure was undertaken to give the following compounds in elution order.

4.7.1. 1,4,5,6-Tetrahydro-3-methyl-1-(2-methyl-1-oxopropyl)-cyclopenta[*c*]pyrazole (8a1) and 2,4,5,6-tetrahydro-3-methyl-2-(2-methyl-1-oxopropyl)-cyclopenta[*c*]-pyrazole (8a2). Overall yield 0.017 g, 9% as a 3:1 mixture.

4.7.2. 2-(2-Benzoyl-2,2-dimethylacetyl)-2,4,5,6-tetrahydro-3-methylcyclopenta[*c*]pyrazole (9a). White solid (0.119 g, 30%), mp 84–85°C (EtOH). ^{1}H, ^{13}C and COLOC NMR: Table 7. IR (nujol) ν_{max} 1730, 1670 cm^{-1}. EIMS *m/z* (%) 297 (23, M+1$^+$), 269 (9), 268 (55), 228 (100), 226 (70), 219 (14), 211 (14), 199 (80), 191 (14) 121 (91), 106 (77), 105 (100), 91 (28). Anal. calcd for $C_{18}H_{20}N_2O_2$ (396.37): C, 72.95; H, 6.80; N, 9.45. Found: C, 72.90; H, 6.69; N, 9.32.

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