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CYCLOADDITION OF N-ACYLIMINES WITH CYCLOBUTADIENES [1]

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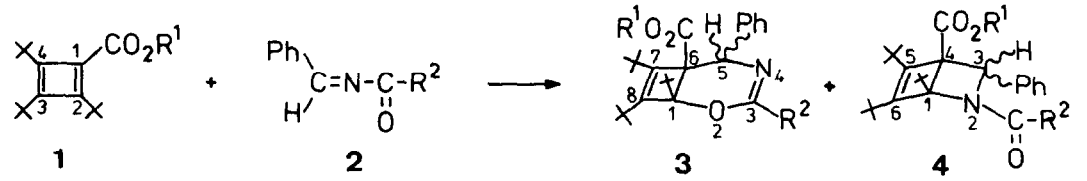
Summary: N-Acylimines (2) possess the characteristics of both hetero-1,3-dienes and dienophiles. They react with the kinetically stabilised cyclobutadienes 1 to form 4-aza-2-oxabicyclo[4.2.0]octa-3,7-dienes (3) and/or 2-azabicyclo[2.2.0]hex-5-enes (4). Compounds of the type 3 undergo acid-catalysed isomerisation to give compounds 4. Homocyclopropenylium intermediates of the type 5 are supposed to be involved in both processes (1 + 2 → 3 + 4 and 3 → 4).

The kinetically stabilised cyclobutadienes 1a [2] and b [3] show a marked readiness for cycloaddition reactions; thus, 1b undergoes photochemical [4] or thermal [5] addition with carbonyl compounds to form 2-oxabicyclo[2.2.0]hexenes or 3-oxatricyclo[3.1.0.$0^{2,6}$]hexanes; [3+2]-cycloadditions with diazo compounds to give Δ^1-pyrazolines [6] are also known. In the present study we were interested in the question as to whether N-acylimines (2) [7] react as heter-1,3-dienes or as dienophiles with 1 [8].

Depending on the substitution pattern of the reactions partners 1 and 2, the reaction (pentane or benzene, 20-80°C, 1 hour to 8 days, ^{1}H-NMR monitoring), produces mixtures of 4-aza-2-oxa-bicyclo[4.2.0]octa-3,7-dienes and 2-azabicyclo[2.2.0]hex-5-enes (3c,d/4c,d), which can be separated by column chromatography (Woelm silica gel, 0.06-0.2 mm, hexane/ether, 4/1) or, alternatively, only one of the two isomeric cycloadducts (3a,b,e or 4f) (see Table 1). Both reactants, therefore, can act as both the 1,3-diene or as the dienophile.

The presence of an intact carbon-carbon double bond bearing two tert-butyl groups is apparent from the only small differences in the chemical shifts in the ^{13}C-NMR spectra of the carbon atoms C-7/C-8 and C-5/C-6 in 3 and 4, respectively (see Table 1) [9]. These data leave no doubt that C-1 and C-2 or C-1 and C-4 of the cyclobutadienes 1 are involved in the cycloaddition. On the other hand, a high field shift of the original azomethine protons in all of the ^{1}H-NMR spectra (δ = 8.43 - 8.92 in 2 compared to δ = 4.90 - 6.09 in 3 or 4) shows that the imine carbon atom is involved in the cycloaddition process. Finally, the resonances for C-3 of the cycloadducts of the type 3 and the CO-amide carbon atoms of the isomers 4 are characteristic; the bridgehead carbon atoms also exhibit

significant differences in the ^{13}C-NMR spectra (see Table 1).



1	a	b
R^1	Me	^tBu

2	a	b	c	d
R^2	Me	$CH_2{}^tBu$	OMe	Ph

3,4	a	b	c	d	e	f
R^1	Me	Me	^tBu	^tBu	^tBu	^tBu
R^2	$CH_2{}^tBu$	Ph	Me	$CH_2{}^tBu$	Ph	OMe

Table 1. Yield, melting points and ^{13}C-NMR data for cycloadducts 3 and 4.

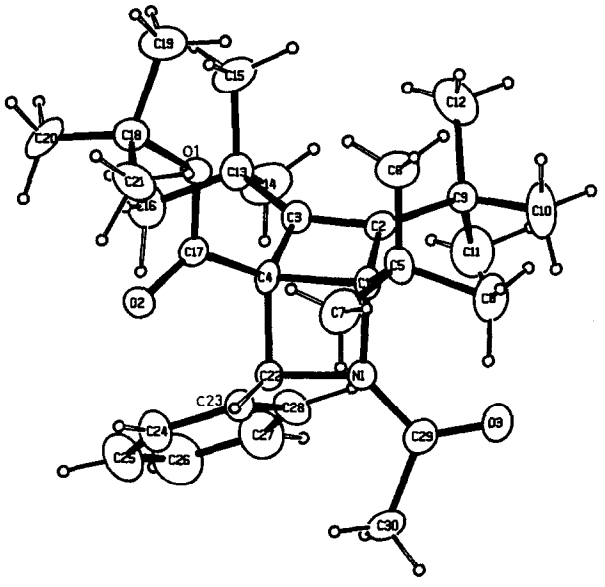
Bicycl. Comp.	Yield [%]	m.p. [°C][a]	^{13}C-NMR ($CDCl_3$, δ in ppm, TMS) C-1/C-6 or C-1/C-4	C-7/C-8 or C-5/C-6		CO-Amid	C=N
3a	51	130	92.2	67.8	150.5	152.2	—	161.2
3b	70	131	93.4	70.1	151.3	152.6	—	157.6
3c [b]	—	oil	—	—	—	—	—	—
3d	56	113	92.8	69.6	150.8	153.0	—	161.5
3e	60	134	93.6	71.6	151.1	152.9	—	157.7
endo-4a [c]	84	166	86.2	59.1	149.6	158.4	172.0	—
endo-4b [c]	60	159	86.1	59.0	149.9	158.6	170.2	—
exo-4c [d]	7	142	87.2	57.9	154.4	158.6	170.1	—
endo-4c [c]	49	166	86.8	59.9	149.7	157.1	169.5	—
exo-4d [d]	10-24	147	87.3	57.9	159.3	168.0	170.5	—
endo-4d [c]	100	176	86.2	59.7	149.9	157.9	171.9	—
endo-4e [c]	84	145	86.3	60.5	150.1	158.1	170.0	—
endo-4f [d]	20	133	85.7	60.7	150.3	155.5	156.8	—

[a] Colourless crystals (if necessary recrystallised from pentane). [b] Not yet obtained in analytically pure state. [c] Obtained by isomerisation of 3. [d] Obtained from the reaction of 1 with 2.

While the configuration at C-5 of the 4-aza-2-oxabicyclo[4.2.0]octa-3,7-dienes 3 remains open, this question can be answered for the 2-azabicyclo[2.2.0]hex-5-enes 4 by ^{1}H-NMR

spectrometry (see also Ref.[5]). In the case of an endo phenyl group, the resonance of the 5-tert-butyl group is affected by the anisotropic shielding of the phenyl group and shifted to higher field (4f: $\delta = 0.70$ compared with 1.25 or 1.47 for the 1- and 6-tert-butyl groups). When the phenyl group is exo, instead of the above mentioned phenomenon, the resonance of the ester tert-butyl group is shifted to higher field (e.g. for 4c $\delta = 1.38$ as compared to 1.53 for 4f).

When the 4-aza-2-oxabicyclooctadienes 3a-e are dissolved in chloroform containing a catalytic amount of trifluoroacetic acid, they are isomerised within a few days to the endo-2-azabicyclohexenes 4a-e (see Table 1) which could not be obtained directly from the reactions of 1 with 2. The above defined ^{1}H-NMR criteria for endo-4f are all fulfilled by these products (4a-e: δ = 0.67-0.72 for 5-tert-butyl, δ = 0.92-1.63 for 6- and 1-tert-butyl groups).

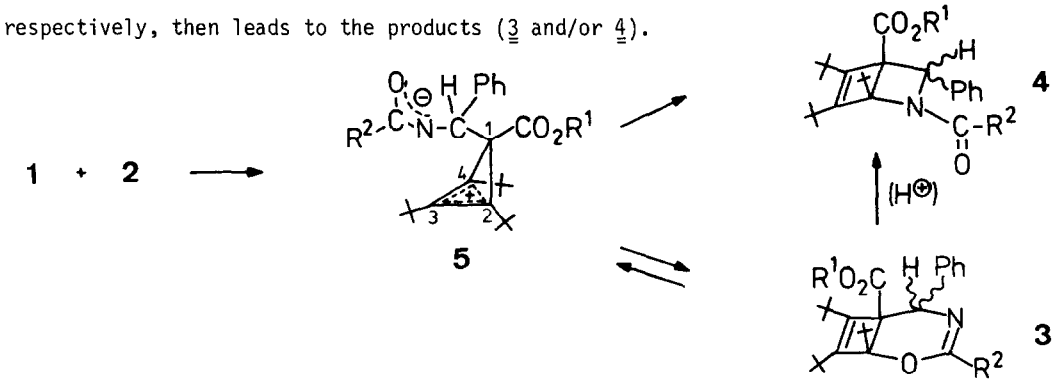


In order to confirm the constitution of the bicyclic compounds 4 and the configuration at C-3, an X-ray structural analysis of the product assigned as endo-4c was performed [10]. This study confirmed fully the assignment derived from the NMR spectra (see Figure 1). The bridging bond C-1 - C-4 [1.612(9) Å] is 0.06 Å longer than that in azetidine [11]. This can be attributed to steric hindrance and additional ring strain resulting from the annelation of the cyclobutene ring.

Figure 1. ORTEP-Plot of tert-Butyl-2-acetyl-1,5,6-tri-tert-butyl-endo-3-phenyl-2-azabicyclo[2.2.0]hex-5-ene-4-carboxylate (endo-4c)

We suppose that the reaction 1 + 2 → 3 and/or 4 is not a concerted process and that the homocyclopropenylium betaines 5 are intermediates [12], i.e., that the reaction starts by nucleophilic attack of C-1 in 1 at the azomethine carbon atom of 2, the charge in 5 being sufficiently stabilised. Ring closure between the anionic oxygen or nitrogen with C-2 or C-4

respectively, then leads to the products (3 and/or 4).



The acid-catalysed isomerisation 3 → 4 should follow an analogous course: H^+ addition to ring oxygen of 3 followed by cleavage of the C/O-bond leads to protonated 5 [-N=C(OH)R^2 in place of -N=C(-O$^-$)R^2], which, after deprotonation, is responsible for the ring closure to 4.

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9 If the reaction products contain a further carbon-carbon double bond with tert-butyl and ester groups, Δδ values of about 20 ppm are to be expected: c.f. Ref.[3].

10 Crystal data: $C_{30}H_{45}NO_3$; monoclinic space group $P2_1/n$; a = 9.846(3) Å, b = 27.071(5) Å, c = 11.272(4) Å, ß = 111.56(2)°; Z = 4, D_{calc} = 1.111 g cm^{-3}. Data collection: Enraf-Nonius CAD 4 (monochromatized Mo Kα radiation). In the range of $2 < \theta < 22$ deg, 3422 unique reflections were measured. 2096 reflections with $I > 2\sigma(I)$ (unit weights) were used in the refinement procedure. Final R values: R = 0.074, R_w = 0.078.
The atomic coordinates, tables with bond and angles, as well as a list of structure factors for this work are available on request from the Director of the Cambridge Cristallographic Data Center, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW, United Kingdom. Any request should be accompanied by the full literature citation for this communication.

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