Tetrahedron Letters Vol. 21, pp 4503 - 4506
0040-4039/80/1115-4503$02.00/0

METHYLKETENE, A MINOR BUT HIGHLY REACTIVE BYPRODUCT IN THE PYROLYSIS GAS OF ACETONE

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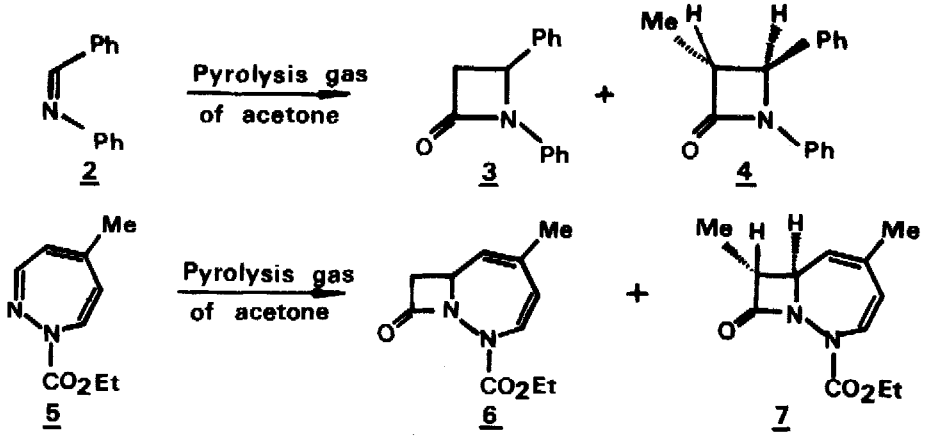
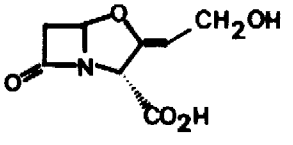
Summary. Methylketene was identified during the pyrolysis of acetone, and proved to be much more reactive than ketene : METHYL-β-LACTAMS were the dominant cycloaddition products when imines are reacted with the pyrolysis gas of acetone at ROOM TEMPERATURE.

In an attempt to synthesize analogues of clavulanic acid 1 (1), a custom-built "ketene lamp" was used in order to produce ketene during the pyrolysis of acetone (2,3). The pyrolysis gas was then reacted in a second vessel with imine derivatives like benzylidene aniline 2 and diazepine 5 (2). The corresponding azetidinones 3 and 6 were obtained, but rather unexpectedly, the major cycloaddition products proved to be the METHYL-AZETIDINONES 4 and 7 respectively. Azetidinone 4 was a known β-lactam (4) having the right H-3/H-4 coupling constant in its NMR spectrum (J=2.5 Hz). As to the structure of 7, it could easily be deduced from its IR [($CHCl_3$) ν (C=O) 1770] and from its ^1H NMR spectrum (5) [($CDCl_3$) δ 1.40 (CH_3 at C-8 ; d; J=7.5 Hz), 2.66 (H-8;qd; J=2.0 and 7.5 Hz), 4.1 (H-7; m)]. Furthermore azetidinone 7 could be obtained independently by letting react diazepine 5 with propionic acid chloride in the presence of triethylamine (albeit in 18% yield only).



To our best knowledge the formation of methyl-azetidinones has not been described so far when the pyrolysis gas of acetone was reacted with imine deriratives (6). Staudinger synthesized the non-methylated azetidinone 3 by this method and did not isolate the corresponding methyl-β-lactam 4 (7); it should be noted however that, benzilidene aniline 2 had been heated up to 200°. In our experiment the pyrolysis gas of acetone was flushed through a melt of 2 kept at 54°. With these latter experimental conditions we obtained a 4/3 ratio of 1.5 (overall yield : 25 %). Furthermore when the pyrolysis gas of acetone was introduced into a hexane solution of diazepine 5, the ratio of the two azetidinones 7/6 was 2.6 (overall yield 88%) at room temperature and 0.45 (overall yield 87%) at 55°. Results obtained with other diazepines at various temperatures led to similar results : non methylated azetidinones were the major products at higher temperatures, whereas the methylated azetininones became the predominant ones when the temperatures were lowered. Eventually when Staudinger's experiment was reproduced à 200° azetidinone 3 was obtained almost exclusively, 4 being formed only in trace amounts as determined by HPLC (8).

The question then arises as to the origin of the methyl group in 4 and in 7. The four-carbon atom diketene was a most unlikely precursor. Indeed reaction of diketene with diazepine 5 in the presence of triethylamine at 20° gave oxazinone 8 (60% yield) as the only detectable adduct (9,10). Furthermore the



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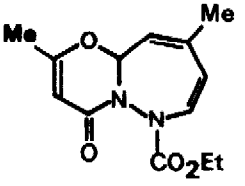

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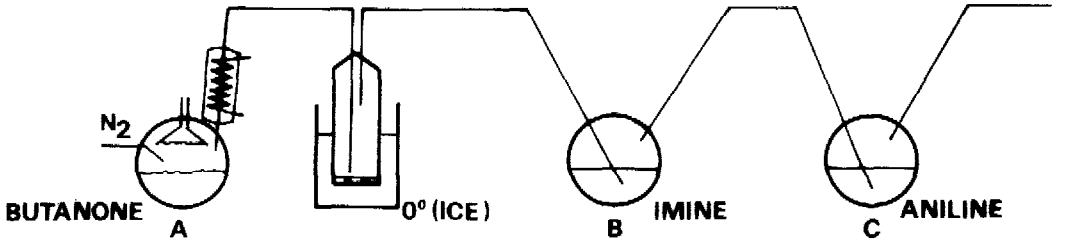
pyrolysis gas of diketene, when reacted with diazepine 5 gave only the non-methylated β-lactam 6. The most likely candidate was methyl-ketene. This was indeed the case and shown as follows. The pyrolysis gas of acetone was flushed into a CH_2Cl_2 solution of aniline which is known to react quickly and quantitatively with any ketene (11). It turned out that only acetanilide was formed at the beginning of the pyrolysis. After two hours though propionanilide was detected by HPLC, the relative amounts of acetanilide and of propionanilide being 99.6 % and 0.4 %.

How could only trace amounts of methylketene lead to the formation of the predominant methyl-β-lactams when reacted with imines at the lower temperatures and which product is the precursor of methylketene ?

Butanone proved to be the answer to the second question : i) butanone was detected by HPLC, in the refluxing acetone; it was separated from acetone by distillation and thence characterized; HPLC showed that the concentration of butanone built up with time; ii) pyrolysis of pure butanone by means of our ketene lamp, followed by trapping of the pyrolysis gas with aniline, led

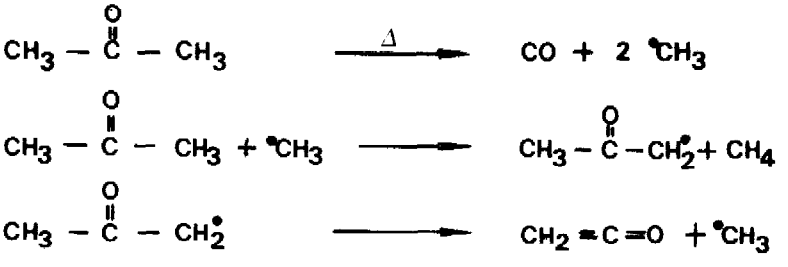
to a 7/3 mixture of acetanilide and of propionanilide (12);iii) when the pyrolysis gas of butanone was reacted with 5 at 20° as above, ONLY THE β-LACTAM-ADDUCT 7 was formed (yield : 81%) (13). This last experiment gives already part of the answer to the first question which we raised above : AT ROOM TEMPERATURE METHYLKETENE REACTS AT A MUCH FASTER RATE WITH IMINES THAN KETENE DOES. This conclusion could be corroborated by the experiment depicted in SCHEME 1 : the pyrolysis gas of butanone, after condensation of

SCHEME 1

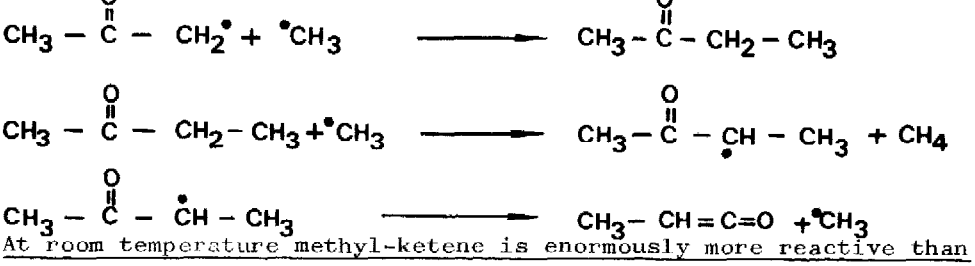


the remaining butanone in the ice-trap, was flushed through reaction vessel B containing a hexane solution of an imine at room temperature and thence through reaction vessel C which contained a CH_2Cl_2 solution of aniline. It turned out that methyl-β-lactams were formed in vessel B only whereas vessel C contained acetanilide but no propionanilide. Obviously methylketene reacted to completion in vessel B whereas ketene did not.

The radical chain fragmentation patterns of acetone leading to ketene are known (6)



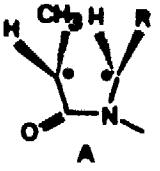
We conclude that methyl-ketene is formed in trace amounts as a result, i) of a chain terminating step, i.e. recombination of an acetone radical and of a methyl radical, and ii) of a hydrogen abstraction followed by a fragmentation according to the mechanistic scheme depicted below :



At room temperature methyl-ketene is enormously more reactive than ketene with imines. When the temperature of these two-step cycloaddition

reactions is raised, the difference in reactivity between methyl-ketene and ketene diminishes.

Although type B zwitterionic intermediates are usually postulated to occur on the reaction pathway leading from imines to the corresponding azetidinones (14), we tend to conclude from our experiments that the methyl-β-lactams are formed via a type A diradical intermediate whose stability and therefore reactivity should be greatly enhanced when compared with those of B. (15).



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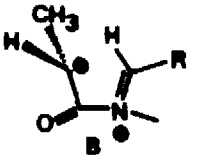

B

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2) Staudinger used the set-up described by J. Schmidlin and M. Bergman, Ber., 43, 2821 (1910) : acetone was distilled through a heated horizontal tube filled with broken porcelain. In our experiments dull-red Ni-Cr wire was fixed at close proximity above the boiling acetone (3), the pyrolysis gas being flushed through an ice-trap before entering vessel B (Scheme 1)

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7) H. Staudinger, Ber., 50, 1037 (1917).

8) 10μ SPHERISORB ODS columns were used throughout for HPLC analyses.

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10) All new compounds gave satisfactory elemental analyses.

11) H. Staudinger, "Die Ketene", F. Enke, Verlag. Stuttgart, 1912; C.C. McCarney and R.S. Ward, J. Chem. Soc. Perkin I, 1600 (1975).

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13) This method is vastly superior to the propionic acid chloride one.

14) J.D. Roberts and C.M. Sharts "Organic Reactions", Volume 12, A.C. Cope et al., Ed. John Wiley and Sons, New-York, N.Y., chapter 1, 1962

15) We thank professor H. Kwart, University of Delaware (USA), for some fruitful discussions.

(Received in France 1 September 1980)