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THE ACYLATION OF 5H-2,3-BENZODIAZEPINES

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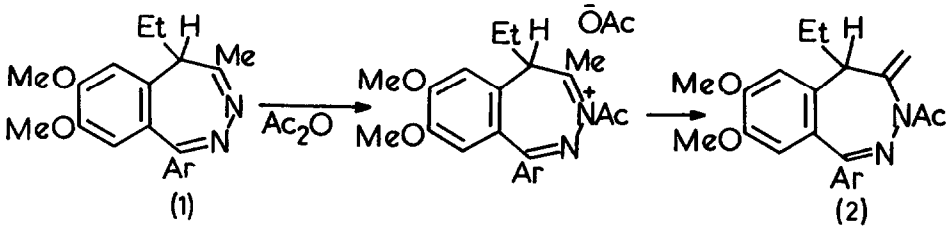
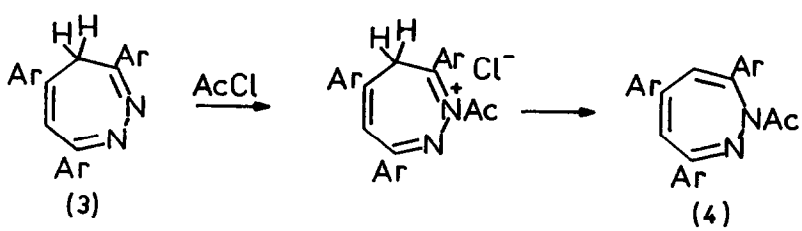
Abstract: The products obtained from the acylation of 4-phenyl-5H-2,3-benzodiazepine (5) are strongly dependent on the nature of the acylating agent and the reaction conditions. Reaction with acid anhydrides followed by a nucleophile gives the 1-substituted 2-acylbenzodiazepines (10) and (11) while reaction with acyl or sulphonyl halides either induces a ring transformation to give the 3-phenylisoquinoline N-imine salts (12) or results in the formation of the acylated dimer (13) via a dehydrochlorinated intermediate (15).

The reactivity of 5H-2,3-benzodiazepines to electrophilic reagents has not been much studied. The only report[1] is concerned with the reactions of the highly substituted example (1) with acylating agents, Scheme 1. Its reactions are interesting because the reaction path to give (2) differs from that followed by the analogous monocyclic system[2] (3), Scheme 2. Whereas the latter react via loss of a ring proton to give the fully unsaturated acylated diazepines (4) the former prefers to lose a proton from the methyl substituent to give the methylene derivative (2).



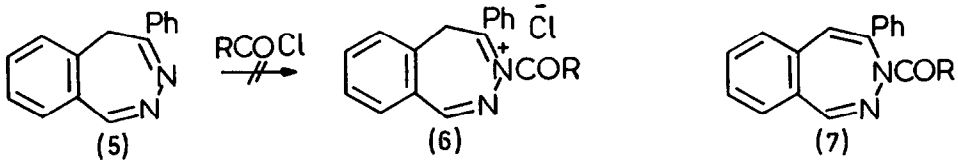
Ar = 3,4-dimethoxyphenyl

Scheme 1



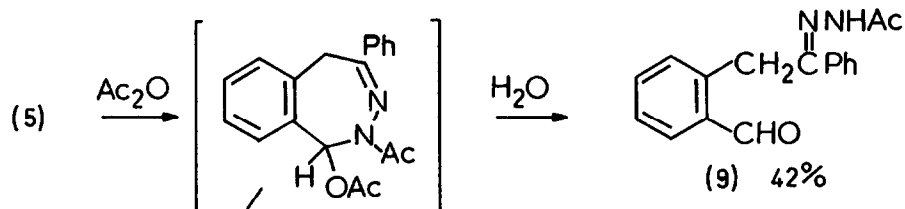
Scheme 2

This letter is concerned with the acylation of 4-phenyl-5H-2,3-benzodiazepine[3] (5), a substrate for which the reaction path followed in Scheme 1 is blocked by the presence of the phenyl group. We thought it likely that it would react in a manner similar to (3) to give (7), a ring system which was of interest to us in connection with another project.[4] However, products of this type were not obtained and it was found that the course of the reaction depended strongly on both the nature of the acylating reagent and the reaction conditions.

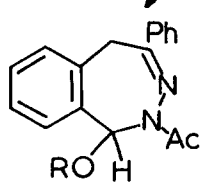


(5) (6) (7)

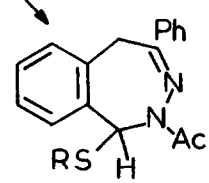
The reaction of (5) with acetic anhydride in benzene was rapid at room temperature and gave a reactive intermediate formulated as (8). This on quenching with water gave (9), but it could also be reacted with a range of O or S nucleophiles to give products e.g. (10) and (11) in which the diazepine ring was retained.[5] Similar results were obtained with propionic anhydride but no reaction was obtained with benzoic anhydride even at reflux temperature.



R	%
(a) Me	88
(b) Et	81
(c) Ph	92



(10)



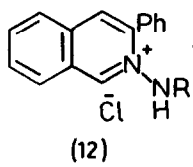
(11)

R	%
(a) Et	62
(b) Ph	64

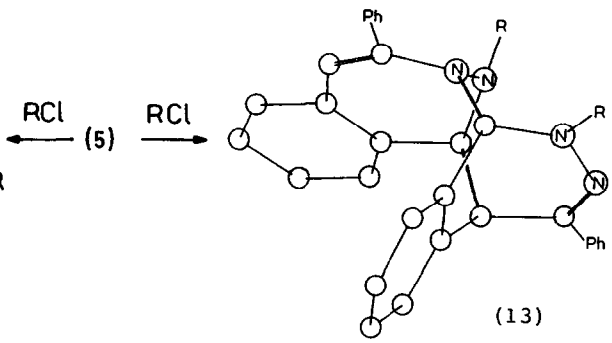
The reaction of (5) with acyl and sulphonyl halides was more complex and the nature of the product depended on both the nature of the reagent and the way in which the reaction was carried out. Addition of acetyl or benzoyl chloride to a solution of the diazepine in benzene at room temperature resulted in the rapid, clean precipitation of the 3-phenylisoquinoline N-imine salts (12a,b).[7] Similar reactions were also carried out with sulphonyl halides and chloroformic esters to give for example (12c,d,e), but in these cases this was the major reaction path only if the benzodiazepine solution was added slowly to an excess of the electrophilic reagent. If the reaction was carried out by adding the reagent

slowly to the diazepine solution (so that the diazepine was in excess for most of the reaction time) then about half of the diazepine was converted to its hydrochloride and the major product was the dimeric species (13). Interestingly the reaction with acetyl chloride also took this as the major reaction path when done at 0°C, giving (13, R=COMe).[8] Under these conditions a deep brown colour was generated as the acetyl chloride was added which faded to colourless over ca 5-10 min. The reaction with benzoyl chloride at 0°C produced a similar brown colour but it was more persistent and lasted for ca 1 h; however in this case no dimer was obtained, only the isoquinoline imine salt (12b, 95%).

R		%
(a)	MeCO	67
(b)	PhCO	89
(c)	CO_2Me	88
(d)	CO_2Et	85
(e)	p-$MeC_6H_4SO_2$	62

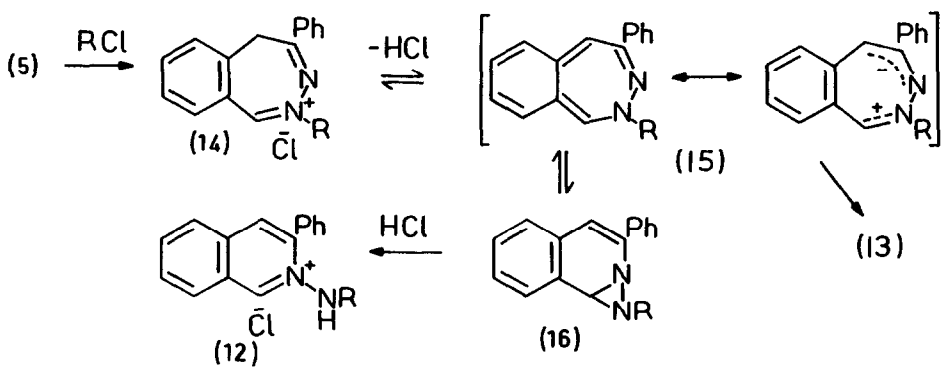


(12)



(13)

These observations can largely be accommodated by the mechanism shown in Scheme 3.



Scheme 3

In view of the formation of (10) and (11) in the acetic anhydride acylation it seems likely that the primary product is the iminium salt (14). This loses a proton to give the species (15) which can then react by two competing pathways; (a) ring contraction to the diazanorcaradiene (16) which finally undergoes an acid catalysed ring opening to give the isoquinoline N-imine salt (12), or (b) a (6π + 4π) dimerisation to give (13). It would appear that the ease of

deprotonation of (14), and the rates of the two competing pathways for (15) are affected by the nature of the substituent R on nitrogen, so leading to the observed variations in behaviour with different electrophilic reagents. These will be discussed in more detail in the full paper. Two other observations are of interest, and support the above general scheme: (i) in the acetic anhydride acylation, treatment of the primary product (8) with a solution of hydrogen chloride in benzene gave (12a) in good yield; and (ii) in the acylation with benzoyl chloride the use of pyridine at -20°C rather than benzene at room temperature as solvent prevented the rapid formation of (12b), so that (14, R= COPh) could be intercepted by the addition of ethanol to give the benzoyl analogue of (10b) in 70% yield with only 13% of (12b).

Further work on the mechanism of this reaction and on the cycloaddition reactions of (15) is in progress. This investigation has not yet been extended to other substituted 5H-2,3-benzodiazepines, but thienodiazepines analogous to (5) i.e. 2-phenyl-1H-thieno[2,3-d][1,2]-diazepine and 4-phenyl-5H-thieno[3,2-d][1,2]-diazepine[3] gave reactions with acetic anhydride followed by ethanol quenching which exactly paralleled those of (5).

We thank the S.R.C. for support (D.P.M.).

References and Notes

1. M. Lempert-Sreter, Acta Chim.Acad.Sc.Hung., 1974, 83, 115.
2. D.J. Harris, G. Y-P. Kan, V. Snieckus, and O. Buchardt, Synthesis, 1975, 603.
3. D.P. Munro and J.T. Sharp, J.C.S.Perkin I, 1980, 1718.
4. P.N. Anderson and J.T. Sharp, J.C.S.Perkin I, 1980, 1331.
5. All new compounds gave satisfactory analytical data. The n.m.r. spectra of (10) and (11) are consistent with the structures assigned e.g. the ^1H spectrum of (10b) showed the C-5 methylene group as an AB system: δ_A 3.85, δ_B 4.95, J_{AB} 15Hz; and the C-1 proton as a singlet at δ6.90. The strong deshielding of the C-1 proton is similar to that observed (δ6.69) for the analogous proton in a 1-ethoxy-2-benzoylisoquinoline derivative.[6]
6. B.C. Uff, J.R. Kershaw, and S.R. Chhabra, J.C.S.Perkin I, 1974, 1146.
7. Compounds (12a-e) gave satisfactory analytical data and their treatment with aqueous alkali gave 3-phenylisoquinoline N-acyl- or N-sulphonyl-imines e.g. (12b) gave 3-phenylisoquinoline N-benzoylimine (85%) m.p. 182-183°C, ν_{max} 1600 cm^{-1} (C=O), identical with an authentic sample prepared via the amination of 3-phenylisoquinoline.
8. The structure of (13, R=COMe) was determined by X-ray diffraction, R.O. Gould and M.D. Walkinshaw, unpublished work.

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