Tetrahedron Letters, Vol.22, No.26, pp 2431 - 2434, 1981
Printed in Great Britain

0040-4039/81/262431-04$02.00/0

RING OPENING AND CLOSING REACTIONS OF IMIDAZOLES AND OTHER 1,3-DIAZAHETEROCYCLES WITH VINYL CHLOROFORMATE AND PHENYL CHLOROFORMATE

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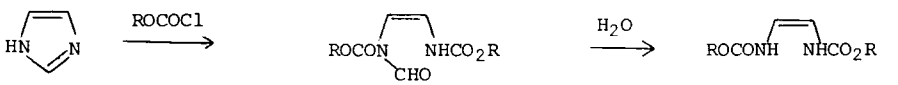
Summary: Treatment of imidazole and benzimidazole with vinyl chloroformate or phenyl chloroformate in weakly alkaline aqueous solution leads to their conversion into the corresponding imidazol-2-ones; in weakly acidic solutions these chloroformates convert adenine into isoguanine, 6-methylaminopurine into 1-methylisoguanine and pyrimidine into an acyclic product.

We have previously described[1] and investigated the kinetics and mechanism[2] of the Bamberger cleavage of imidazoles on their treatment in aqueous solution at neutral pH with the protein modifying reagent diethylpyrocarbonate and with ethyl chloroformate (Scheme 1, R=Et). As an extension of this work we were interested to examine the effect of an analogous reagent containing

Scheme 1



1a, R=Et
1b, R=CH=CH$_2$

2a, R=Et
2b, R=CH=CH$_2$

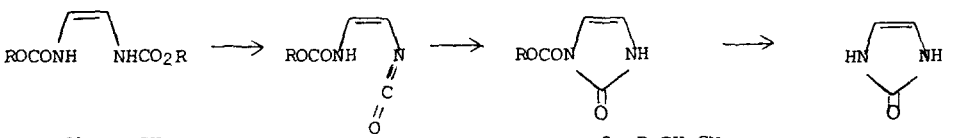
a better leaving group, OR, in the hope that the facile removal of this group from 2 would permit further chemistry through the thus uncovered amine functionality. In the present paper we describe our initial investigations along these lines which have led to a novel, mild, and single step transformation of imidazoles into imidazol-2-ones. Other 1,3-diazaheterocycles may also undergo similar reactions as seen below for example in the conversion of adenine into isoguanine.

Initial experiments were performed with vinyl chloroformate (PCR Research Chemicals, Inc., used as received). With this reagent imidazole could be quantitatively converted into its Bamberger cleavage products, 1b and 2b,[3] by the two methods previously described[2] for 1a and 2a, although in the present case a pH of 6.0 was maintained for both methods. Compound 2b in dilute aqueous solution at pHs between 7 and 10 was, unlike 2a, unstable, as indicated by the complete and rapid, particularly at higher pH, disappearance of UV absorption by such solutions above 220

nm. The nature of this reaction was investigated by proton NMR spectroscopy. The NMR spectrum of a 10 mM solution of 2b in 1/1 $^2H_2O/^2H_3$-CH_3CN containing 0.1 M $NaHCO_3$ was followed over several days at room temperature. The spectral features attributable to 2b[3] disappeared rapidly (1-2 hrs) leaving a monovinyloxycarbonyl derivative (deduced by integration of the vinyl vs imidazole derived protons) with the following spectrum: (^2H_2O) δ 7.33(dd,J=7,14 Hz, 1, OCH=CH_2), 6.92 (d,J=4 Hz, 1, CON-CH=), 6.59(d,J=4 Hz, 1, HN-CH=), 5.17(dd,J=1, 14 Hz, 1, OCH=CH), 4.86(dd,J=1,7 Hz, 1, OCH=CH). This spectrum disappeared more slowly (days) leaving a final spectrum containing only a sharp singlet at δ 6.46.[4]

These observations were rationalized in terms of Scheme 2 where the final product is identified as imidazol-2-one and the intermediate, 3, as 1-vinyloxycarbonylimidazol-2-one. The reaction is shown to go by way of an isocyanate intermediate because of the (low) pKa[5] of the

Scheme 2



2b, R=CH=CH_2 3, R=CH=CH_2

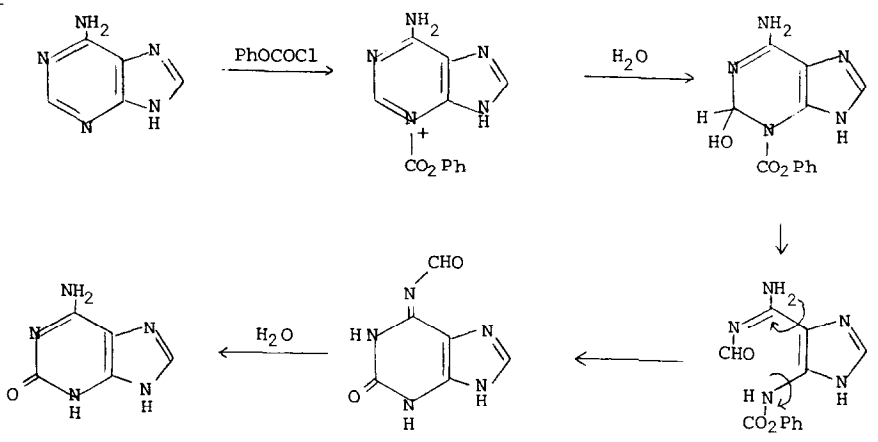
vinyl alcohol leaving group[6]. After reaction on a larger (20 mg) scale, accelerated to completion by heating on a steam bath for 1 hour, the product solution was evaporated to dryness and a white crystalline solid isolated by vacuum sublimation (150°/0.1 mm). This material had identical NMR and IR spectra, mp and mmp to authentic imidazol-2-one.[7]

To a stirred solution of benzimidazole (1.18 g, 10 m mole) and sodium bicarbonate (3.36 g, 40 m mole) in 100 mL of 50% aq THF at 0° was added vinylchloroformate (2.65 g, 25 m mole). After 1 hour at 0° the solution was refluxed for 1 hour. Evaporation of the THF then yielded a solid which was isolated by filtration and recrystallized from 50% aq EtOH. This crystalline material, mp 136-137°, is believed, on the basis of its NMR spectrum [C^2HCL_3, δ 7.89 (d,J=8 Hz, 1, N-CH-N), 7.0-7.6 (m, 5, Ar-H, OCH=CH_2), 5.25 (dd, J=1, 15 Hz, 1, OCH=CH), 4.86 (dd, J=1, 7 Hz, 1, OCH=CH)] to be 1-vinyloxycarbonylbenzimidazol-2-one. It was hydrolyzed further in 50% aq EtOH containing 2 equivalents of sodium carbonate by heating to reflux for 1 hour. The precipitate formed on cooling had the melting behavior, IR and NMR spectrum of benzimidazol-2-one. Yields on both steps were essentially quantitative. Imidazole could also be converted preparatively to imidazol-2-one in this way although conditions for the quantitative crystallization of the product from the final solution were not pursued. It was also possible to achieve the same results using the cheaper phenyl rather than vinyl chloroformate. In this case the phenol byproduct was removed by benzene extraction.

Since Leonard and coworkers[9] have previously shown that treatment of certain nucleic acid bases, notably adenine, with diethylpyrocarbonate can also lead to ring opening reactions. We examined the reactions of adenine and pyrimidine with vinyl and phenyl chloroformates. Treatment of adenine (1.0 g, 7.4 m mole) in 100 mL of 50% aq THF with phenyl chloroformate (2.82 g, 18 m

mole) at room temperature and at pH 4.5[9] (maintained by NaOH addition) yielded after 1 hour a white precipitate which after drying exhibited mp, IR, NMR and mass spectra and paper chromatographic behavior (iPrOH: $NH_4OH:H_2O$::7:1:2) identical to those of an authentic sample of isoguanine, 4 (Vega Biochemicals). The reaction here is proposed to follow Scheme 3 which, subsequent to the initial acylation, has features similar to the well-known Dimroth rearrangement of 6-aminopurines.[10]

Scheme 3



4 5

Recyclisation (5 → 4) is suggested to occur here through nucleophilic attack by the originally exocyclic nitrogen because similar treatment of 6-methylaminopurine with phenyl chloroformate yielded 1-methylisoguanine[11] rather than 6-methylaminopurine-2-one. The inability of the N-formylimino nitrogen to initiate cyclisation is further demonstrated by the conversion of pyrimidine into the acyclic product, 3-vinyloxycarbonylaminoprop-2-en-1-al[13] on treatment with vinyl chloroformate at pH 4.5; purine yielded no bicyclic product either under these conditions

These facile conversions may be of interest to protein and nucleic acid chemists.

Acknowledgement: We are grateful to the National Institutes of Health for financial support.

Footnotes and References

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3. Although 1b, an oil, was only identified by its NMR spectrum (C^2HCl_3, δ 9.38 (s, 1, CHO), 7.2-7.4 (m, 2, OCH=CH_2), 6.75 (dd, J=7, 11 Hz, 1, NH-CH=), 5.52 (d, J=7 Hz, 1, >N-CH=), 4.5-5.1 (m, 4, OCH=CH_2)), which is completely analogous to that of 1a[2], 2b, a colorless crystalline solid, mp 123-124° (from 1/1 benzene/hexane) was completely characterised: UV (H_2O) λ_{MAX} 242 nm (20,500); NMR (C^2HCl_3) δ 8.96 (br d, J=8 Hz, 2, NH), 7.30 (dd, J=7, 15 Hz, 2, OCH=CH_2), 5.91 (dd, J=2, 8 Hz, 2, NH-CH=, collapses to singlet on ^2H_2O exchange), 4.76 (dd, J=1, 15 Hz, 2, OCH=CH), 4.49 (dd, J=1, 7 Hz, 2, OCH=CH); IR (KBr) 3400, 3140, 1800, 1730, 1660 cm^{-1}. Anal. calc'd for $C_8H_{10}N_2O_4$: C, 48.48; H, 5.09; N, 14.14. Found:

C, 48.46; H, 4.98; N, 14.07.

4. Presumably the acetaldehyde from the vinyloxycarbonyl groups had either evaporated from the solution or exchanged with solvent deuterium and been oxidised.
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11. The position of the methyl group in the product (NMR (NaO^2H) δ 7.83 (s, 1, ArH), 3.47 (s, 3, CH_3); mass spectrum, m/e 165 (100%, M^+)) was determined by acid hydrolysis[12] to 1-methylxanthine (NMR (NaO^2H) δ 7.65 (s, 1, ArH), 3.39 (s, 3, CH_3); mass spectrum, m/e 166 (100%, M^+), 109 (48%, $M-CH_3NCO$)[12]).
12. A.F.Cook, R.T.Bartlett, R.P. Gregson and R.J.Quinn, J.Org.Chem., 45 4020-4025 (1980).
13. This compound, vacuum sublimed, mp 124-6°, was characterised by the following: NMR (C^2HCl_3) δ 10.56 (brd, J=12 Hz, 1, NH), 9.52 (d, J=8 Hz, 1, CHO), 7.72 (dd, J=12, 15 Hz, 1, NH-CH=), 7.30 (dd, J=7, 15 Hz, 1, OCH=CH_2), 5.94 (dd, J=8, 15 Hz, 1, =CHCHO), 4.94 (dd, J=1, 15 Hz, 1, OCH=CH), 4.67 (dd, J=1, 7 Hz, 1, OCH=CH); IR (KBr) 3100(br), 2960, 1735, 1600(br) cm^{-1}; mass spectrum, m/e (relative intensity, %) 141 (6, M^+), 98 (100), 96 (11), 70 (28). Anal. calc'd for $C_6H_7NO_3$: C, 51.07; H, 5.00; N, 9.93. Found: C, 49.52; H, 5.02; N, 9.70.

(Received in USA 2 March 1981)