HETEROCYCLES, Vol. 3, No. 9, 1975

TRANSFORMATIONS OF 1,3-DISUBSTITUTED URACIL-CARBENE ADDUCTS RING EXPANSION TO 1,3-DIAZEPINE DERIVATIVES.

Herman P.M. Thiellier[1], Gerrit-Jan Koomen and Upendra K. Pandit*.

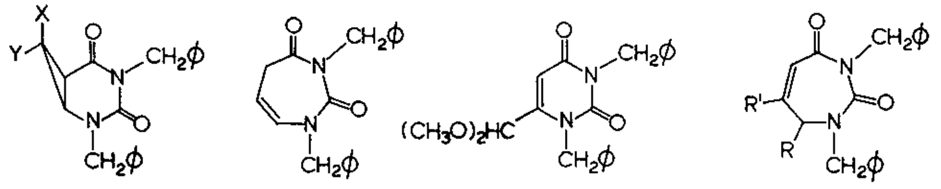
Organic Chemistry Laboratory, University of Amsterdam, Nieuwe
Achtergracht 129, Amsterdam, The Netherlands.

A facile conversion of uracil-carbene adducts (1) to diazepinediones (2) is described.

In a previous paper[2] we have reported a convenient procedure for the preparation of carbene adducts of general structure 1. This communication presents the synthesis of substituted 2,4-dioxo-1,3-diazepines 2 via ring expansion of the latter adducts.

Indication that suitable halo adducts (1) could be ring-expanded thermally was based upon the spectroscopic recognition (NMR) of 2a in the mixture obtained by heating 1a in decalin. The product 2a was, however, too unstable to allow its isolation in a pure state. In order to convert the reaction product "in situ" into a more stable derivative, the reaction was repeated in methanol at 110° (sealed tube, 5h), whereupon 1,3-diazepine derivative 2b was formed in 34%[8] yield [2b: IR[3] 1630, 1650, 1680 cm^{-1}; PMR[3], δ 2.78 s (3H, OCH$_3$), 4.71 d, J=1.5 (1H, H$_7$), 6.30 d, J=1.5 (1H,

Scheme I

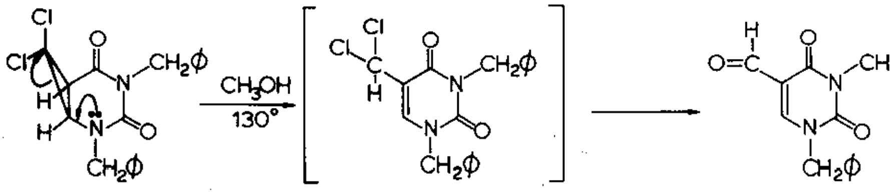


1 3 4 2

a X = Y = Cl
b X = Y = Br
c X = Y = H
d X = H , Y = Cl
e X = Cl , Y = F
f X = F , Y = Cl

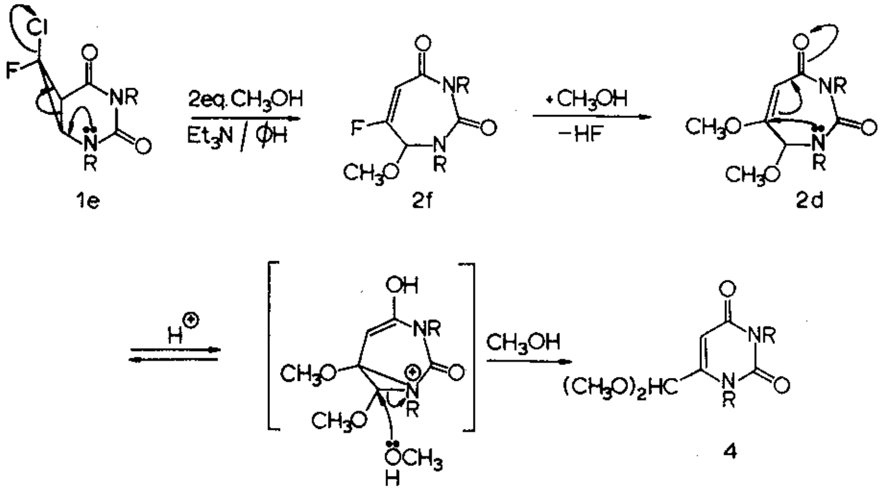
a R = R' = Cl
b R = OCH_3 , R' = Cl
c R = OCH_3 , R' = Br
d R = R' = OCH_3
e R = R' = H
f R = OCH_3 , R' = F
g R = $OC(CH_3)_3$, R' = F

Scheme II



1a 5 6

Scheme III



1e 2f 2d 4

H_5), 4.85 and 4.59, AB pattern J=15 (2H, N_1-CH_2), 5.00 and 5.40. AB pattern J=15 (2H, N_3-CH_2)]. The high field chemical shift of the methoxy group is presumably due to the shielding effect of the aromatic rings. When dibromide 1b was allowed to react under the same conditions, 2c was formed in quantitative yield.

In an effort to improve the extent of conversion of 1a (to 2b) the adduct was heated (130°, 24h) in methanol containing 2 eq. of triethylamine. The latter was added to trap the acid formed during the reaction. Separation of the reaction mixture (SiO_2, ethyl acetate/cyclohexane 1:3) gave, in addition to the anticipated product 2b (39%), 2d (13%) and the pyrimidine aldehyde 6 (19%). [2d: IR 1640, 1680 cm^{-1}, PMR δ 2.77 s (3H, C_7-OCH_3), 3.50 s (3H, C_6-OCH_3), 4.52 d, J=2 (1H, H_7), 5.21 d, J=2 (1H, H_5), AB patterns of benzyl methylene protons at 4.68, 4.75, 4.97 and 5.41. MS m/e 367 (M^++1), 366 (M^+) . 6: IR: 1715, 1695, 1660, 1610 cm^{-1}; PMR δ, 5.00 s (2H, N_1-CH_2), 5.15 s (2H, N_3-CH_2), 8.04 s (1H, H_6), 10.00 s (1H, aldehyde)]. Formation of 2d can be readily explained by addition of methanol to 2b followed by elimination of HCl. For the genesis of aldehyde 6, ring-opening leading to 5 seems an essential step. The latter is presumably hydrolyzed during the work-up of the mixture (Scheme II).

Attempts to reduce 1a with tri-n-butyltinhydride (3 eq.) at 135° (6 h) yielded (SiO_2, ethyl acetate/cyclohexane) three products: 1d (12%), 2e (8%) and 3 (21%). No 1c could be detected in the reaction mixture. [2e: IR 1640, 1670, 1700, 1720 cm^{-1}. PMR δ 3.63 d, J=7 (2H, H_7), 4.58 s, 5.12 s, (4H, benzyl methylene), 6.12 d, J=10 (1H, H_5), 6.47 AB pattern, J=10, lower field proton splits into triplets J=7 (1H, H_6), 3: IR 1660, 1710 cm^{-1}; PMR δ 3.05 d, J=7 (2H, H_5), 4.71 s, 5.02 s, (4H, benzyl methylene), 5.51 q, J=7 (1H, H_6), 6.00 d, J=7 (1H, H_7)][7]. The identification of isomers 2e and 3 is, in view of characteristic differences in their IR spectra, significant for the structural assignment of all the 1,3-diazepine derivatives reported in this communication.

For the synthesis of 5-fluorouracil- or 5-fluorouridine- homologues, the ring expansion of the chloro-fluoro carbene adducts 1e and 1f[2] were of particular interest. Heating the *endo*-chloro adduct 1e , in methanol, (110°, 5h), gave, besides 2d (30%)[8], a new product (30%)[8] to which, based upon its spectral data, structure 4 has been assigned. [4 $UV_{max}(CH_2Cl_2)$ 268 (8600); PMR δ 3.25 s (6H, OCH_3), 4.96 s (1H, acetal proton), 5.19 s (2H, N_1-CH_2), 5.26 s (2H, N_3-CH_2), 6.10 s (1H, H_5)]. The structure of 4 was attested by its hydrolysis (aq. acetic acid) to 1,3-dibenzyl-6-formyluracil[4]. Under the same reaction conditions the *exo*-chloro isomer 1f was recovered unchanged. The aforementioned results are in agreement with the theoretical considerations of an electrocyclic ring-opening reaction[5]. A concerted disrotatory cyclopropane ring-opening is sterically prohibited in the case of the *exo*-chloro adduct[6]. Furthermore, since the allyl cation formed during the electrocyclic reaction would be stabilized by a neighbouring nitrogen atom and destabilized by a carbonyl group, ring-openings in *endo*-chloro adducts would be expected to give 1,3-diazepine derivatives of general structure 2 rather than 3. This indeed corresponds to the observed results.

Since HCl is liberated in the reaction of 1e in methanol, the possibility that 4 might be formed from 2d under acidic conditions was investigated. Treatment of 2d with p-toluenesulphonic acid in methanol yielded 4 quantitatively. This fact supports the aforementioned suggestion. Formation of 4 may be rationalized to proceed via an aziridinium intermediate as indicated in Scheme III. Heating 1e in methanol/triethylamine suppressed the secondary reaction and gave 2d exclusively, in high yield. (Scheme III).

For the synthesis of fluorine substituted 1,3-diazepines the reactions leading to 2d and 4 have to be suppressed. This could be conveniently achieved by heating 1e (110°, 10 h) in benzene with a limited amount (2 eq) of methanol and a calculated quantity of triethylamine. Purification by TLC (SiO_2) yielded 83% of 2f [IR: 1640, 1670, 1700 cm^{-1}; PMR δ 2.82 s, (3H, OCH_3), 4.66 dd, J_{HH}=1.5, J_{HF}=13 (1H, H_7), 5.85 dd, J_{HH}= 1.5, J_{HF}=13 (1H, H_5), 4.86, 4.57, 5.40, 4.94, 2 AB systems (benzylmethylene)]. Treatment of 2f with excess methanol/triethylamine at 90° yielded 2d, as expected, at a rate considerably higher than that of the direct transformation of 1e into 2d under the same conditions; thereby supporting the assumption that 2f is an intermediate in the process 1e ⟶ 2d. The secondary reaction of 2f involving addition of methanol, followed by elimination of HF, could conceivably be suppressed by employing a sterically hindered alcohol. This was supported by the observation that in t-butanol/triethylamine (110°, 2.5 h) 1e was converted quantitatively into the 6-fluoro-1,3-diazepine system 2g.

Application of the ring expansion reaction to addition products of various carbenes to suitably protected uridine derivatives[2] is being currently investigated.

REFERENCES

*To whom all inquiries should be addressed.

1 Taken in part from the forthcoming doctorate thesis of H.P.M. Thiellier, University of Amsterdam.

2 H.P.M. Thiellier, A.M. van den Burg, G.J. Koomen and U.K. Pandit, Heterocycles, 1974, **2**, 467.

3 All IR and NMR spectra were recorded in $CHCl_3/CDCl_3$ respectively.

4 K.Y. Zee-Cheng, C.C. Cheng, J. Heterocycl.Chem., 1967, **4**, 163.

5 R.B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry", Verlag Chemie/Ac. Press, 1970, 47.

6 L. Ghosez, G. Slinckx, M. Glineur, P. Hoet and P. Laroche, Tetrahedron Letters, 1967, 2773.

7 Compare the N,N-dimethyl analog, T. Kunieda, B. Witkop, J.Amer. Chem.Soc., 1971, **93**, 3478.

8 Yields calculated from NMR spectra of the mixture.

Received 5th July, 1975