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SELECTIVE FORMATION AND HYDROLYSIS OF DERIVATIVES OF 4-IODO-3-UREIDO-1-BUTANOL

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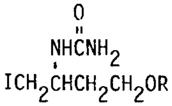
As part of our investigation into the mechanism of biotin catalysis[2] we needed to prepare appropriately O-substituted derivatives of 4-iodo-3-ureido-1-butanol (1a). In this communication we wish to report on aspects concerning the synthesis and subsequent hydrolysis of these substrates.



$$\begin{array}{c} \mathrm{O} \\ \| \\ \mathrm{NHCNH_2} \\ | \\ \mathrm{ICH_2CHCH_2CH_2OR} \end{array}$$

1a R=H

b R=$COCH_3$

c R=THP

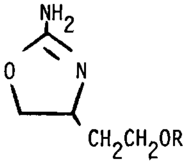
d R=CH_2Ph

The title compounds[3] were readily prepared in high yield from commercially available 3-buten-1-ol (2a). Initial protection of the alcohol function of 2a according to established procedures[4] gave the corresponding O-substituted derivatives 2b (bp 120°C, [75%]) and 2c (bp 183°C, [90%]). Subsequent treatment of an ether suspension of the alkene and AgNCO with I_2 afforded the corresponding β-iodo isocyanates.[5] These adducts were not isolated but were directly converted to the desired β-iodo ureas 1b[6] and 1c[7] in 95% and 80% yields, respectively, by passing ammonia through a pre-filtered ether solution containing the isocyanate. Noteworthily, examination of the NMR spectrum for each of these two β-iodo ureas indicated that the reaction had occurred with complete regiospecifity to give the Markovnikov product. The exclusive formation of this adduct was surprising in light of previous results obtained for 1-hexene.[5] Hassner and collaborators have shown that INCO adds to this olefin to give both the Markovnikov and the anti-Markovnikov products, despite the electrophilic nature of this reagent.[5,8]

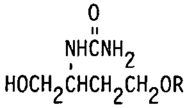
$CH_2 = CHCH_2CH_2OR$

2a R=H
b R=$COCH_3$
c R=THP
d R=CH_2Ph

An indication of the controlling factors responsible for the unusually high regiospecifity of these reactions was ascertained from the subsequent treatment of 1b and 1c with water. This procedure has been previously used to convert β-iodo ureas to the 2-amino oxazolines,[9,10] and was introduced in the present study to provide additional evidence for our structural assignments Surprisingly, when a suspension of 1b or 1c in water was gently boiled under reflux (2h) neither the expected oxazolines 3 nor the corresponding 4-hydroxy-3-ureido derivatives 4 were obtained.



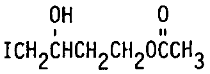
3a R=H
b R=$COCH_3$
c R=THP
d R=CH_2Ph



$$HOCH_2\overset{\overset{\displaystyle O}{\| }}{}\!\underset{}{\overset{NHCNH_2}{CH}}CH_2CH_2OR$$

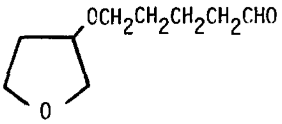
4a R=H
b R=$COCH_3$
c R=THP
d R=CH_2Ph

Instead the sole producted isolated in 58% yield from 1b was 3-hydroxy-4-iodobutyl acetate (5), while the 3-substituted tetrahydrofuran derivative 6 was obtained from 1c in 67% yield.[11] In each case, preferential hydrolysis of the ureido moiety had occurred.



$$ICH_2\overset{OH}{C}HCH_2CH_2O\overset{O}{\overset{\|}{C}}CH_3$$

5



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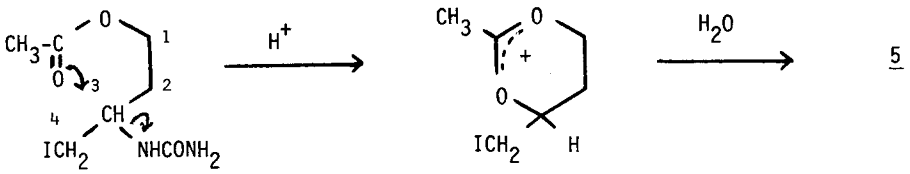
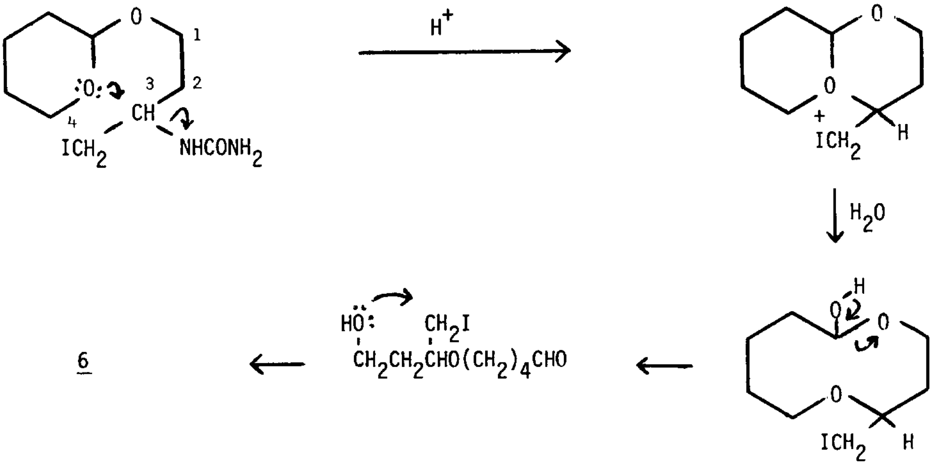
The unexpected ease of displacement of the ureido group in these two reactions suggests that anchimeric assistance is provided by the oxygen atom of the protecting group in the hydrolysis step. Potential mechanisms for the conversion of 1b → 5 and 1c → 6 are given in Schemes 1 and 2, respectively. In both cases, the reaction is envisioned to proceed through a six-membered transition state with the incipient carbonium ion at carbon-3 being stabilized by the oxygen atom as well as the β-iodo group.

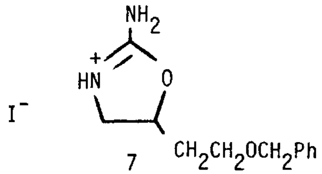
Scheme 1



Scheme 2



This neighboring group participation by the oxygen atom may also be responsible for the high regiospecitity observed in the preparation of the β-iodo ureas 1b and 1c. Here again, the oxygen is situated five atoms removed from an initially formed cyclic iodonium species.[12] The presence of this atom should help stabilize an incipient carbonium at carbon-3, thereby leading to the preferential formation of the Markovnikov product. In an effort to test this hypothesis we prepared 2d (bp 118°C (34 mm)). This alkene like 1-hexene should yield a mixture of iodo ureas. Interestingly, when an ether suspension of 2d and AgNCO was treated with I_2, a very rapid uptake of the I_2 was noted; however, when ammonia was bubbled through the pre-filtered solution no iodo urea precipitated. Upon refrigeration overnight a crystalline material formed whose spectral and analytical data was consistent[13] with structure 7 (mp 92-93°C).[14] The formation of this oxazolinium salt can easily be rationalized if neighboring group participation by the benzyl ether oxygen atom now stabilizes the incipient carbonium at carbon-4 through a five-membered transition state. Preferential stabilization of this carbonium ion would lead to the anti-Markovnikov iodo isocyanate. Conversion of this material to the corresponding iodo urea followed by cyclization would yield 7.



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References and Notes

1. Alfred P. Sloan Fellow, 1977-1979. Camille and Henry Dreyfus Teacher-Scholar Grant Recipient, 1977-1981.

2. H. Kohn, J. Am. Chem. Soc., 98, 3690 (1976).

3. All new compounds reported herein had satisfactory spectral (NMR, IR, and MS) and analytical (elemental analysis or high resolution MS) data in accord with the assigned structure.

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6. Partial spectral data 1b:ir (KBr) 1670-1700 cm^{-1}; NMR (DMSO-d_6) δ 1.36-1.80 (m, 2H), 1.52 (s, 3H), 3.23-3.29 (m, 2H), 3.58-4.16 (m, 3H), 5.20-5.85 (broad s, 2H), 6.40-6.56 ppm (broad s, 1H).

7. Partial spectral data 1c: ir (KBr) 1665 cm^{-1}; NMR (DMSO-d_6) δ 1.14-1.96 (m, 8H), 3.18-3.82 (m, 7H), 4.84-5.21 (m, 1H), 5.32-5.64 (broad s, 2H), 6.24-6.50 ppm (m, 1H).

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11. Compound 5 can be converted to the corresponding epoxide (bp 90°C (22 mm)) by treatment with NaH in ether (66% yield). This epoxide proved to be identical in all respects with an authentic sample prepared by the addition of 1.4 equivalents of m-chloroperbenzoic acid to a methylene chloride solution of 2b (79% yield). The aldehyde 6 was fully characterized in terms of its 2,4-dinitrophenylhydrazone derivative (mp 80°C: Partial spectral data: ir (KBr) 1625 cm^{-1}; NMR ($CDCl_3$) δ 1.58-2.22 (m, 6H), 2.30-2.64 (m, 2H), 3.36-4.28 (m, 7H), 7.44-8.42 (m, 3H), 9.08-9.12 (d, J=$3H_z$, 1H), 10.6-11.0 ppm (broad s, 1H)).

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13. S. P. McManus, J. T. Carroll, and C. U. Pittman, Jr., J. Org. Chem., 35, 3768 (1970).

14. Partial spectral data 7: ir (KBr) 1680, 1620 cm^{-1}; NMR (DMSO-d_6) δ 1.90-2.17 (q, J=7Hz, 2H), 3.42-3.58 (m, 1H), 3.52-3.65 (t, J=7Hz, 2H), 3.79-3.97 (t, J=10Hz, 1H), 4.49 (s, 2H), 5.03-5.34 (m, 1H), 7.32 (s, 5H), 8.73-9.36 ppm (broad s, 3H).

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