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HYPERVALENT ORGANOIODINE REAGENTS IN THE β-FRAGMENTATION OF BICYCLIC CARBINOLAMIDES LEADING TO IMIDES

R. Hernández, J.J. Marrero, D. Melián[a], and E. Suárez*

Instituto de Productos Naturales Orgánicos del C.S.I.C., 38206-La Laguna, Tenerife, Spain.
[a]Departamento de Química Orgánica, Universidad de La Laguna, Tenerife, Spain.

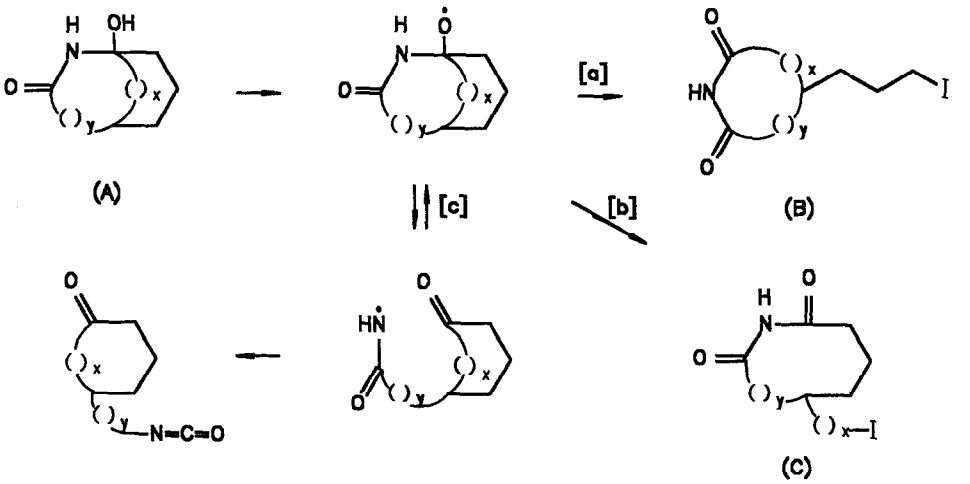
Summary: A mild and convenient method for the synthesis of 3,4-substituted cyclic imides by photolysis of bicyclic [3.3.0]- and [3.2.1]-carbinolamides in the presence of (diacetoxyiodo)-benzene and iodine is described.

Previous communications from this laboratory described the synthesis of lactones[1] and anhydrides[2] through β-fragmentation of alkoxy radicals generated by photolysis of hemiketals and lactols, respectively, in the presence of (diacetoxyiodo)-benzene and iodine. Continuing our interest in this field we envisaged the synthesis of cyclic imides from carbinolamides using this methodology (Scheme, A→B or C).

Nowadays there is considerable interest in cyclic imides and their N-derivatives, on account of their significance not only as reagents[3], but also as useful intermediates, *via* N-acyliminium ions, for the synthesis of pyrrolizidine alkaloids[4], and as starting material for the synthesis of chlorins, assumed intermediates in the biosynthesis of vitamin B_{12}.[5] Furthermore cyclic imides are present in the structures of several naturally occurring compounds such as isohematinic acid,[6] sesbanimide,[7] and showdomycin.[8]

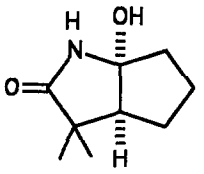
Cyclic imides can be synthesized by cyclization of a variety of bifunctional derivatives such as amidic acid, diamides and dinitriles, usually involving the formation of a bond between a carbonyl carbon and a nitrogen.[9] Novel methodology for the general synthesis of 3,4-substituted cyclic imides is desirable.

There are a number of simple ways to prepare some types of carbinolamides such as 1-hydroxy-2-azabicyclo[3.3.0]octan-3-one and 1-hydroxy-2-azabicyclo[3.2.1]octan-3-ona from α,β-unsatu-

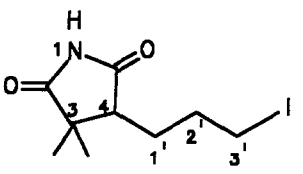


Scheme

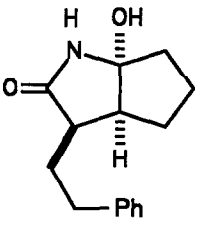
rated carbonyl compounds.[10] Substrates required for the present study were prepared in one of two ways. In the first route, readily available conjugated enones[11] were converted directly into carbinolamides (**1**)[12] and (**3**)[13] utilizing the Lapworth procedure.[14] In the second, steroidal carbinolamides (**6**)[15], (**9**)[15] and



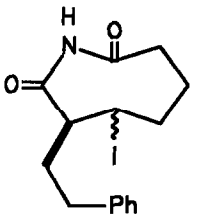
(1)



(2)



(3)



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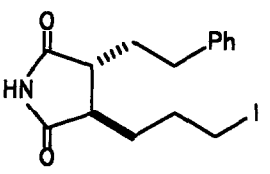

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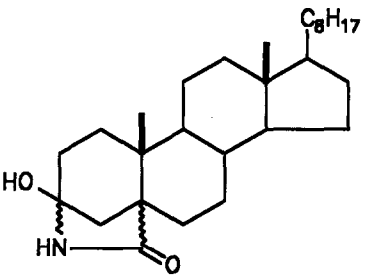
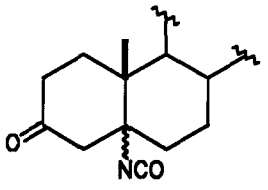


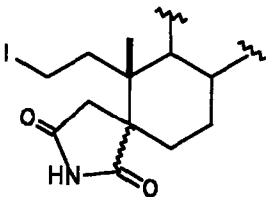
(6) 3β-NH, 5β

(9) 3α-NH, 5α



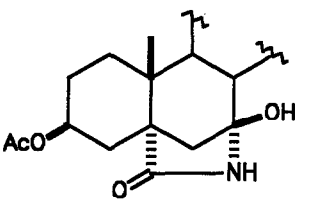
(7) 5β

(10) 5α



(8) 5β-CO-

(11) 5α-CO-



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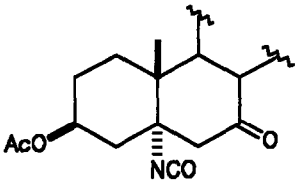

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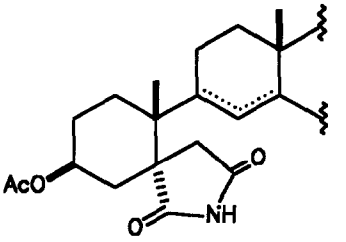

(14)

(12)[16] were obtained from the corresponding α,β-unsaturated carbonyl compounds by reaction with Et_2AlCN[17] and hydrolysis of the nitrile intermediates.[15]

Results are summarized in the table. In practice, the reaction proceeds smoothly in mild conditions with

good yields, and a typical experiment is described as follows: a solution of carbinolamide (**1**) (1 mmol) in methylene dichloride (50 ml) containing (diacetoxyiodo)-benzene (DIB) (1.5 mmol) and iodine (1 mmol) was irradiated with two 100-W tungsten-filament lamps for 1 h at 25-30 °C. The reaction mixture was then poured into water and extracted with CH_2Cl_2. The organic layer was washed with aqueous sodium thiosulphate and water. Rotative chromatography (Harrison-chromatotron) of the residue gave the imide (**2**)[18] in 61% yield (entry 1).

TABLE. Radical fragmentation of bicyclic carbinolamides.[a]

Entry	Substrate	Reagent[b] (mmol)	Conditions Time(h)	Temp.(°C)	Products (yield %)
1	**1**[12]	1.5/1	1	25-30	**2**[18](61)
2	**3**[13]	1.5/1	0.5	20	**4**[19](41)[c], **5**[21](39)
3	**6**[15]	1.5/1	1.5	25	**7**[22](20), **8**[23](62)
4	**9**[15]	1.5/1	1	25	**10**[24](19), **11**[25](63)
5	**12**[16]	1.9/1.1	1.5	25	**13**[26](32), **14**[27](38)

[a] Compounds (**1**) and (**3**) were synthesized as racemic compounds, [b]Mmoles of (diacetoxyiodo)-benzene/mmoles of iodine per mmol of substrate; [c] Mixture of two isomeric iodoimides (8:2).

A plausible mechanism for this reaction is shown in the scheme (path a).

The reaction performed with the carbinolamide (**3**)[13] deserves special attention. In this case, medium sized imides (**4**)[19] were also obtained through ring expansion as occurred with hemiketals[1] (path b; x = 0, y = 1) (entry 2).

Complete regioselectivity was observed, however, in the fragmentation of the steroidal carbinolamides (**6**), (**9**), and (**12**) to give the more stable 5-membered imide, isocyanates being formed, as a side reaction, in theses cases, probably by amidyl rearrangement (path c; x = 1, y = 0) (entries 3- 5).[20]

In view of its operational simplicity and efficiency, the method described above will hopefully prove to be of synthetic utility. Our further investigation on this reaction will be reported in due course.

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13. Compound (3): m.p. 162-163 °C (ethyl acetate); IR ($CHCl_3$) ν_{max} 3580, 3400, 1680 cm^{-1}; ^{1}HNMR (200 MHz, $CDCl_3$) δ 1.4-2.8 (12H, m), 6.4, 6.5 (2H, m, m, NH, OH), 7.26 (5H, m, Ar); ^{13}CNMR (50.3 MHz, $CDCl_3$) δ *inter alia* 179.63 (3-C), 96.88 (1-C); MS m/z 245.1438 (M^+, 3%), 141.0791 (M^+-CH_2CH_2Ph+H, 100%).
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16. Compound (12): m.p. 200-201 °C (acetone); $[\alpha]_D$ -50 ° ($CHCl_3$); IR ($CHCl_3$) ν_{max} 3570, 3400, 1700 cm^{-1}; ^{1}HNMR δ *inter alia* 0.70 (3H, s, 13-Me), 0.98 (3H, s, 10-Me), 3.21 (1H, s, OH), 5.66 (1H, m, 3-H), 7.25 (1H, s, NH); ^{13}CNMR δ 179.25 (5-CO), 170.42 (O-CO), 88.31 (7-C), 70.17 (3-C), 53.99 (5-C); MS m/z 487.3646 (M^+, 53%), 444.3489 (M^+-MeCO, 100%).
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18. Compound (2): m.p. 68-69 °C (acetone-n-pentane); IR ($CHCl_3$) ν_{max} 3395, 1775, 1718 cm^{-1}; ^{1}HNMR δ 1.24, 1.35 (3H, 3H, s, s, 3-Me_2), 2.51 (1H, t, J 7.1 Hz, 4-H), 3.26 (2H, m, 3'-H_2), 8.16 (1H, m, N-H); ^{13}CNMR δ 182.77, 178.41 (2-C and 5-C), 6.07 (3'-C); MS m/z 295.0067 (M^+, 26%), 168.0995 (M^+-I, 100%).
19. Compound (4); two isomeric iodoimides which were separated by crystallization : m.p. 133-135 °C (n-pentane); IR ($CHCl_3$) ν_{max} 3335, 1687 cm^{-1}; ^{1}HNMR δ 1.5-3.2 (11H, m), 4.22 (1H, dt, CH-I), 7.24 (5H, m, Ar), 8.20 (1H, m, NH); ^{13}CNMR δ 172.50, 170.51 (2-C and 8-C), 34.06 (4-C); MS m/z 371.0377 (M^+, 6%), 91.0526 (100%), and m.p. 179-180 °C (ethyl acetate); IR ($CHCl_3$) ν_{max} 3340, 1690 cm^{-1}; ^{1}HNMR δ 1.5-2.8 (11H, m), 4.24 (1H, dt, CH-I), 7.25 (5H, m, Ar), 8.13 (1H, m, NH); ^{13}CNMR δ 171.70, 170.12 (2-C and 8-C), 32.30 (4-C); MS m/z 371.0392 (M^+, 1%), 91.0415 (100%).
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21. Compound (5): m.p. 95-96 °C (ethyl acetate); IR ($CHCl_3$) ν_{max} 3385, 1770, 1723, 1705 cm^{-1}; ^{1}HNMR δ 1.6-2.3 (6H, m), 2.54 (2H, m, 3H, 4H), 2.8 (2H, apparent t, -CH_2-Ar), 3.17 (2H, apparent t, -CH_2-I), 7.23 (5H, m, Ar), 8.93 (1H, m, NH); ^{13}CNMR (20.1 MHz, $CDCl_3$) δ 179.70, 179.54 (2-C and 5-C), 5.63 (3'-C); MS m/z 371.0338 (M^+, 12%), 140.0715 (100%).
22. Compound (7): unstable; IR ($CHCl_3$) ν_{max} 2230, 1710 cm^{-1}; ^{1}HNMR δ 0.68 (3H, s, 13- Me), 1.06 (3H, s, 10-Me), 2.18, 3.11 (2H, AB, J 15.2 Hz, 4-H_2); ^{13}CNMR δ 209.12 (3-C), 123.45 (NCO), 68.75 (5-C); MS m/z 427.3444 (M^+, 22%), 384.3345 (100%).
23. Compound (8): m.p. 110-113 °C (methanol); $[\alpha]_D$ +11 ° ($CHCl_3$); IR ($CHCl_3$) δ 3395, 1765, 1715 cm^{-1}; ^{1}HNMR δ 0.66 (3H, s, 13-Me), 1.27 (3H, s, 10-Me), 2.56, 2.78 (2H, AB, J_{AB} 18.8 Hz, 4-H_2), 3.11 (2H, m, 2-H_2), 8.24 (1H, br s, N-H); ^{13}CNMR δ 182.35, 175.79 (5-CO and 4-C), 53.12 (5-C), 0.65 (2-C); MS m/z 555.2546 (M^+, 1%), 428.3517 (M^+-I, 100%).
24. Compound (10): unstable; IR ($CHCl_3$) ν_{max} 2225, 1705 cm^{-1}; ^{1}HNMR δ 0.68 (3H, s, 13- Me), 1.16 (3H, s, 10-Me), 2.30, 2.68 (2H, AB, J 15.2 Hz, 4-H_2); ^{13}CNMR δ 208.46 (3-C), 122.63 (NCO), 68.98 (5-C); MS m/z 427.3467 (M^+, 50%), 384.3435 (100%).
25. Compound (11): m.p. 159-161 °C (methanol); $[\alpha]_D$ -8° ($CHCl_3$); IR ($CHCl_3$) ν_{max} 3390, 1770, 1710 cm^{-1}; ^{1}HNMR δ 0.89 (3H, s, 10-Me), 2.21, 2.88 (2H, AB, J 18.5 Hz, 4-H_2), 3.12 (2H, t, J 9.4 Hz, 2-H_2), 8.14 (1H, br s, N-H); ^{13}CNMR δ 181.90, 176.34 (5-CO and 4-C), 51.85 (5-C), 1.23 (2-C); MS m/z 555.2449 (M^+ 13%), 372.2905 (100%).
26. Compound (13): unstable; IR ($CHCl_3$) ν_{max} 2250, 1725 cm^{-1}; ^{1}HNMR δ 0.66 (3H, s, 13- Me), 1.27 (3H, s, 10-Me), 2.26, 2.80 (2H, AB J 13 Hz, 6-H_2); ^{13}CNMR δ 207.96 (7-C), 170.30 (OCOMe), 123.29 (NCO), 70.05 (5-C), 69.67 (3-C); MS m/z 485.3480 (M^+, 93%), 382.3220 (100%).
27. Compound (14): m.p. 157-158 °C (methanol); $[\alpha]_D$ +27° ($CHCl_3$): IR ($CHCl_3$) ν_{max} 3395, 1765, 1720 cm^{-1}; ^{1}HNMR δ 0.49 (3H, s, 13-Me), 1.17 (3H, s, 10-Me), 2.19, 2.96 (2H, AB, J 18.4 Hz, 6-H_2), 5.37 (1H, m, 3-H), 5.62 (1H, m, 8-H), 7.59 (1H, m, N-H); ^{13}CNMR δ 180.52, 174.99 (5-CO and 7-C), 138.70 (9-C or 14-C), 125.73 (8-C), 69.16 (3-C), 52.54 (5-C); MS m/z 485.3501 (M^+, 48%), 312.2007 (100%).

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