

Hypervalent Organoiodine Reagents in the Transannular Functionalisation of Medium-sized Lactams: Synthesis of 1-Azabicyclo Compounds

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The amidyl radical intermediates, produced by photolysis of medium-sized lactams 7-heptanelactam (**1**), 8-octanelactam (**3**), and 9-nonanelactam (**6**) in the presence of (diacetoxyiodo)benzene (DIB) and iodine, undergo transannular hydrogen abstraction to afford intramolecularly functionalised compounds such as oxoindolizidines (**4**) and (**5**) and the 1-azabicyclo[5.3.0]decan-2-one (**7**) that are obtained in high yield from lactams (**3**) and (**6**), respectively.

Alkaloids incorporating the indolizidine or 1-azabicyclo[5.3.0]decan-2-one (*Cephalotaxus* alkaloids) ring system comprise a rather large group of compounds isolated from diverse natural sources. They are endowed with a vast array of biological effects, hence attracting much attention as targets for organic syntheses.¹

During the past few years we have examined hypervalent iodo-compounds aimed at generating alkoxy² and neutral aminyl³ radicals to promote intramolecular functionalisation of suitably positioned non-activated carbon atoms.⁴

Herein, we describe efficient syntheses of oxoindolizidines (**4**) and (**5**), and of 1-azabicyclo[5.3.0]decan-2-one (**7**), which is a substructure present in many *Cephalotaxus* alkaloids, using a methodology based on the photolysis of medium-sized lactams in the presence of (diacetoxyiodo)benzene (DIB) and iodine.

Transannular functionalisation of medium-sized *N*-chloro-lactams using a modified version of the Hofmann-Löffler-Freytag reaction, induced by silver(I), has been reported to

give oxopyrrolizidine and oxoindolizidine in low yield, which precludes its synthetic application.⁵ The intramolecular functionalisation with primary amidyl radicals led to lactones, *via* imino ether intermediates, as described by Barton⁶ and Petterson.⁷ Nevertheless, in some cases we have observed the formation of lactams.⁸

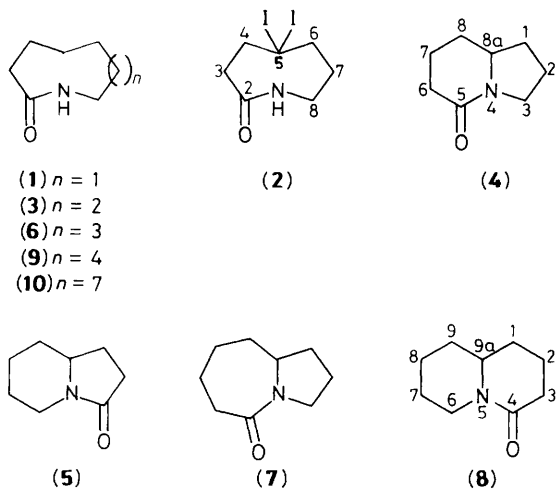
The results are summarized in Table 1. In practice, the reaction proceeds smoothly under mild conditions, and a typical experiment is described as follows. A solution of 8-octanelactam (**3**)† (1 mmol) in cyclohexane (40 ml) containing DIB (1.1 mmol) and iodine (1 mmol) was irradiated with two 100 W tungsten-filament lamps for 4.5 h at 25 °C. The reaction mixture was then poured into water and the organic extracts washed with aqueous sodium thiosulphate and water. Rotative chromatography (Harrison-chromatotron) of the

† Lactams (**1**), (**3**), and (**10**) were purchased (Fluka), and lactams (**6**) and (**9**) were prepared, starting from the corresponding ketones *via* oxime and Beckmann rearrangement.

Table 1. Intramolecular functionalization of lactams.^a

Entry	Lactam	Reagent ^b DIB/I ₂ (mmol)	Temp./°C	Time/h	Product(s)	Yield/%
1	(1)	1.2/1.0	80	1	(2)	40
2	(3)	1.1/1.0	25	4.5	(4) ⁹ (5) ¹⁰	82 14
3	(6)	1.5/1.0	40	1	(7) ¹¹ (8) ¹²	67 13
4	(9)	1.1/1.0	70	4	No reaction	
5	(10)	1.2/1.0	80	7	No reaction	

^a The reactions were performed in cyclohexane (40 ml) under irradiation with two 100 W tungsten-filament lamps. ^b Per mmol of lactam.



residue yielded 5-oxoindolizidine (4)⁹‡ and 3-oxoindolizidine (5)¹⁰ (entry 2),§ the total yield of functionalised compounds being 96%. Both compounds (4) and (5) have been reduced to (±)-δ-coniceine.^{9,10}

The photolysis of 7-heptanelactam (1) deserves special attention since the *gem*-di-iodide (2)¶ (m.p. 109–111 °C) is formed through double hydrogen abstraction (entry 1). This result indicates that the monoiodide formed in the first hydrogen abstraction from C-5 adopts a conformation in which the cyclization step to oxopyrrolizidine is not propitious, a second abstraction of the geminal iodide hydrogen occurring instead.

1-Azabicyclo[5.3.0]decan-2-one (7)¹¹¶ (hydrochloride, m.p. 99–100 °C) was obtained in 67% yield by photolysis of 9-nonanelactam (6), and a small amount (13%) of the isomeric

‡ We are using the Chemical Abstracts numbering system for indolizidines and quinolizidines as shown in (4) and (8).

§ Satisfactory spectral (i.r., ¹H and ¹³C n.m.r., analysis and/or high resolution mass spectrometry) data were obtained for all compounds.

¶ Selected spectroscopic data for (2): i.r. (CHCl₃) 3390, 1655 cm⁻¹; ¹H n.m.r. (CDCl₃, 200 MHz) δ 6.53 (1H, br. s, NH), 3.40 [2H, q (t after addition of D₂O), J 6.8 Hz, 8-H₂], 3.20 (2H, m, 3-H₂), 2.45 (2H, t, J 6 Hz, 6-H₂), 2.27 (2H, m, 4-H₂), 1.67 (2H, dt, J 6.8, 6 Hz, 7-H₂); ¹³C n.m.r. (CDCl₃, 50.3 MHz, DEPT experiment) δ 176.10 (C), 56.82 (CH₂), 48.83 (CH₂), 39.66 (CH₂), 35.51 (CH₂), 35.37 (CH₂), 13.25 (C). For (7): i.r. (CHCl₃) 1620 cm⁻¹; ¹H n.m.r. (CDCl₃, 200 MHz) δ 3.75–3.61 (2H, m), 3.43–3.30 (1H, m), 2.59–2.34 (2H, m), 2.24–2.18 (1H, m), 1.93–1.24 (9H, m); ¹³C n.m.r. (CDCl₃, 50.3 MHz, DEPT experiment) δ 174.22 (C), 58.84 (CH), 46.89 (CH₂), 38.22 (CH₂), 35.73 (CH₂), 34.92 (CH₂), 29.80 (CH₂), 23.39 (2CH₂).

4-oxoquinolizidine (α-norlupinone) (8)¹² was also formed (entry 3).

The transannular hydrogen abstraction observed in these reactions takes place through a six-membered transition state; only the 4-oxoquinolizidine (8) can be formed via a seven-membered transition state. As expected, no reaction was observed with eleven- and fourteen-membered lactams (9) and (10) (entries 4 and 5).

This method should be useful, particularly for the synthesis of more elaborate alkaloids with these skeletons.

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