Palladium(II) Catalysed Construction of Tetrasubstituted Carbon Centres, and Spiro- and Bridged-ring Compounds from Enamides of 2-Iodobenzoic Acids

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Various *N*-vinyl- and *N*-allyl-amides of 2-iodobenzoic acid undergo catalytic cyclisation in the presence of tetraethylammonium chloride and a palladium acetate-based catalyst system to generate a range of synthetically useful structural features including tetrasubstituted carbon centres, and spiro- and bridged-ring compounds, and in which 5-*exo-trig* cyclisations are kinetically favoured.

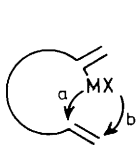
We have been studying the palladium(II) and rhodium(I) catalysed cyclisation of 2-bromo-1,ω-dienes with respect to competition between *exo-trig* (**1a**) and *endo-trig* (**1b**) cyclisation modes,[1] and now report further reactions where such potentially competitive cyclisations provide a facile route for the construction of tetrasubstituted carbon centres and spiro- and bridged-ring systems.

Thus the enamide (**2a**) is cyclised to (**3a**) (57%)† in acetonitrile (80 °C; 2 h) by a catalyst system consisting of palladium acetate (0.1 mol. equiv.), triphenylphosphine (0.2 mol. equiv.), tetraethylammonium chloride (1 mol. equiv.), and potassium carbonate (2 mol. equiv.). The use of a tetra-alkylammonium chloride to facilitate palladium catalysed vinylation of organic halides was introduced by Jeffrey[2] and has proved very useful in our studies. Under similar conditions (**2b**) gave (**3b**) (51%) but the addition of electron donor substituents to the aroyl ring resulted in substantially lower yields. Thus (**2c**) gave (**3c**) (38%) and (**2d**) gave (**3d**) (23%). Ninomiya and co-workers have synthesised (**3c**)[3] and (**3d**),[4] by photocyclisation, as intermediates in the synthesis of the berberine alkaloids tetrahydropalamatine and sinactine respectively. The palladium catalysed route is superior to the photocyclisation for the production of (**3c**) but less efficient for (**3d**).

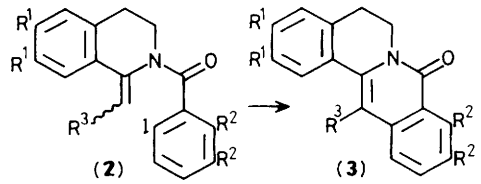
† All yields refer to isolated products. All new compounds gave satisfactory microanalytical and spectral data.

The catalytic cyclisation of (**2a**—**d**) is forced to occur by the 6-*endo-trig* mode since a 5-*exo-trig* cyclisation creates an organopalladium intermediate lacking the necessary β-hydrogen atom for elimination. It was therefore of interest to study the catalytic cyclisation of (**2e**) which was obtained as a mixture of four stereoisomers (olefinic and amide moieties) and in which both 6-*endo-* and 5-*exo-trig* cyclisation can occur. Cyclisation [dimethylformamide (DMF), 100 °C; 1 h] of (**2e**) using palladium (0.1 mol. equiv.), triphenylphosphine (0.2 mol. equiv.), and potassium carbonate (2 mol. equiv.) gave (80%) a 3.9 : 1 mixture of (**4**) and (**3e**). This yield and the selectivity for (**4**) increased using acetonitrile as solvent (80 °C; 1 h) and with the addition of 1 mol. equiv. of tetraethylammonium chloride. In this case a 10 : 1 mixture (91%) of (**4**) and (**3e**) was obtained. Lowering the temperature to 30—50 °C resulted in a further increase in the ratio of (**4**) to (**3e**) to 13 : 1, but the reaction was very slow at these temperatures. The β-carboline (**5**) undergoes an analogous cyclisation to (**2a**) at 80 °C (acetonitrile; 24 h; 1 mol. equiv. of Et_4NCl) to give (**6**) (32%). An angular methyl substituent is generated when (**7**) is cyclised by the palladium acetate catalyst system (DMF; 30 °C) to give a 2 : 1 mixture (72%) of (**8**) and (**9**).

The facile generation of ring junction functionality in (**4**), (**8**), and (**9**) suggests such processes will be of value in natural product synthesis. Intramolecular attack at the more substituted end of the enamide double bond contrasts with the intermolecular reaction where the terminal position is most reactive.[5]

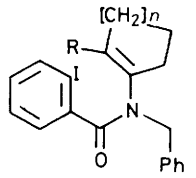


(1)

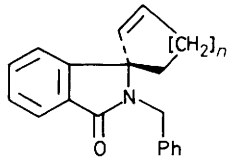


(2) (3)

a; $R^1 = R^2 = R^3 = H$
b; $R^1 = OMe$, $R^2 = R^3 = H$
c; $R^1 = R^2 = OMe$ $R^3 = H$
d; $R^1, R^1 = OCH_2O$, $R^2 = OMe$, $R^3 = H$
e; $R^1 = R^2 = H$, $R^3 = Me$



(10) **a**; $n = 1$, R = H
b; $n = 2$, R = H
c; $n = 3$ R = H
d; $n = 4$ R = H
e; $n = 1$, R = CO_2Et



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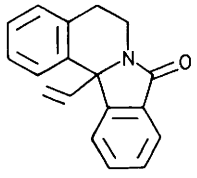

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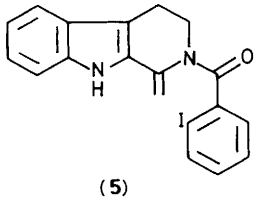

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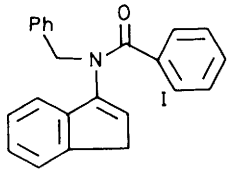

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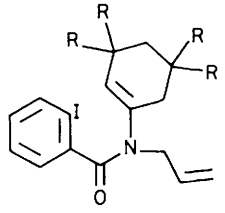
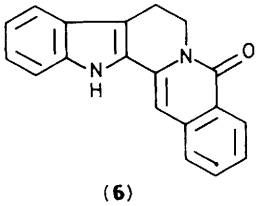
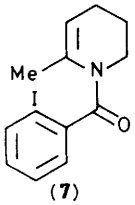


(14) **a**; R = H
b; R = Me



(6)



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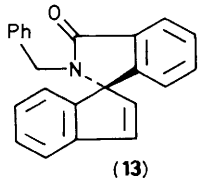

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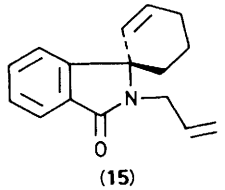

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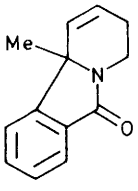

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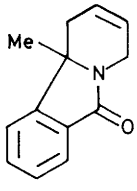

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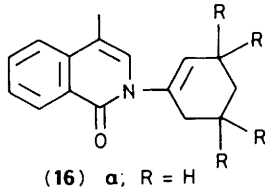
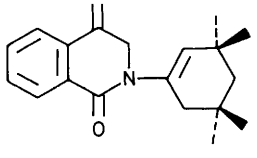


(16) **a**; R = H
b; R = Me



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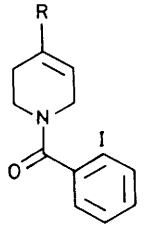
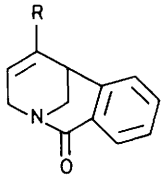


(18) **a**; R = H
b; R = Ph
c; R = Me



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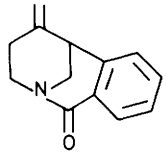

(20)

The kinetic preference for 5-*exo*- as opposed to 6-*endo-trig* cyclisation is also clearly displayed by the enamides (**10a—e**) and (**12**) which all undergo regiospecific 5-*exo-trig* cyclisation (acetonitrile; 50—80 °C) in the presence of 1 mol. equiv. of tetraethylammonium chloride, 0.1 mol. equiv. of palladium acetate, and the appropriate amounts of triphenylphosphine and potassium carbonate. The products are the corresponding spirocyclic compounds (**11a—e**) and (**13**) which are formed in 60—87% yield. No 6-*endo-trig* products were detected in these cases. With prolonged reaction times or higher temperatures some double bond isomerisation occurs. This new cyclisation complements that of Ninomiya and co-workers who photocyclised *N*-benzoyl enamines of cyclohexanones *via* a 6-*endo* process.[6]

The cyclisation of (**14a**) and (**14b**) affords potential competition between 5-*exo*- and 6-*exo-trig* cyclisation modes. In the presence of tetraethylammonium chloride and the palladium acetate catalyst system (**14a**) cyclises (80 °C; 9 h) to give (**15**) (52%) (5-*exo-trig*) together with a small amount (<10%) of (**16a**) (6-*exo-trig*). In contrast (**14b**) in which β-hydride elimination from a 5-*exo-trig* cyclisation is blocked gives (acetonitrile; 50 °C; 3 days) a 7 : 4 mixture (50%) of (**17**) and (**16b**). On prolonged reaction (**16b**) is the sole product.

The palladium acetate catalyst system (including 1 mol. equiv. of tetraethylammonium chloride) is also effective for the construction of bridged ring systems. Thus (**18a**) and (**18b**) cyclise (acetonitrile; 30—80 °C) to give (**19a**) (88%) and (**19b**) (55%) whilst (**18c**) gives (DMF; 110 °C; 1.5 h) a 4 : 1 mixture (70%) of (**20**) and (**19c**).

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References

1 R. Grigg, P. Stevenson, and T. Worakun, *J. Chem. Soc., Chem. Commun.*, 1984, 1073; 1985, 971.
2 T. Jeffrey, *J. Chem. Soc., Chem. Commun.*, 1984, 1287; *Tetrahedron Lett.*, 1985, **26**, 2667.
3 I. Ninomiya, T. Naito, and H. Takasugi, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1720.
4 I. Ninomiya, H. Takasugi, and T. Naito, *Heterocycles*, 1973, **1**, 17.
5 R. F. Heck, *Pure Appl. Chem.*, 1978, **50**, 691.
6 I. Ninomiya, T. Naito, and T. Kiguchi, *J. Chem. Soc., Perkin Trans. 1*, 1973, 2257.