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An Approach to Isoindole Skeleton via ortho Palladation

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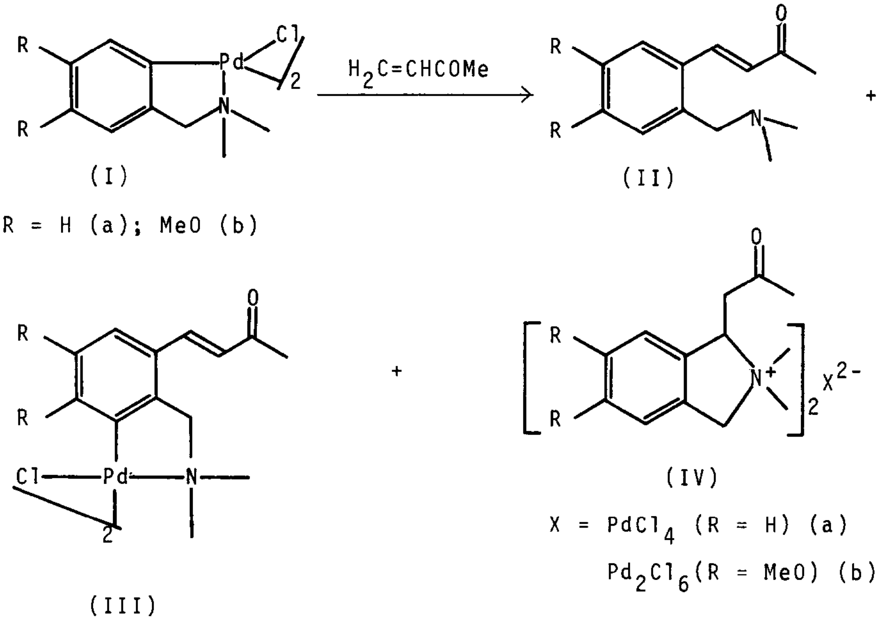
An acid-induced cyclisation of the products of vinylation of ortho palladated NN-dimethylbenzylamines by 3-buten-2-one (II) leads to isoindolinium derivatives (IV) as confirmed by an X-ray structural study.

Cyclopalladated compounds have recently found various applications in organic syntheses, among which routes to heterocycles appear to be very promising.[1] We communicate here a simple approach to isoindolinium salts based on acid-promoted intramolecular amination of activated carbon-carbon double bond of aminoaryl alkene obtained from ortho palladated NN-dimethylbenzylamines (I) and 3-buten-2-one. The reaction between (I) and the enone was first reported by Holton.[2] It was stated that (Ia) and the enone react in



refluxing benzene or toluene in the presence of tertiary amines to afford (IIa) in a more than 90% yield. We failed to reproduce this result. The highest yield obtained by ourselves was 37% (refluxing benzene, 10 h, in the presence of NEt_3). A high yield of (IIa) was achieved, however, using a chloroform-acetic acid mixture as a solvent in the presence of triethylamine. At room temperature after 15 h the yield of (IIa) was 90%. The product was isolated according a procedure similar to that in ref. 3.

When the reaction was carried out under the same conditions but without addition of triethylamine, the yield of (IIa) dropped to 34% and two additional products (IIIa) and (IVa) were formed in 5 and 20% yield, respectively. After the reaction was completed, soluble products (IIa) and (IIIa) remained in solution, while (IVa) precipitated as brown crystals together with palladium metal. The reaction mixture was filtered and to the filtrate water was added. New cyclopalladated compound (IIIa)[4] was isolated as a yellow solid from the chloroform layer by column chromatography (silica gel-chloroform), while (IIa) was extracted with $CHCl_3$ from the water-acetic acid layer after neutralisation by aqueous ammonia. The precipitate was extracted several times with hot methanol or acetonitrile: concentrating the solution provided (IVa)[5] as a brown solid. Dimethoxy-substituted complex (Ib) exhibited a similar behaviour; (IIb),[3] (IIIb), and (IVb)[6] were obtained in 51, ca. <2, and 21% yield, respectively, under identical conditions. Complexes (III) are formed via the ligand exchange reaction[7] between primary products (II) and starting compounds (I). ^{1}H NMR data give sufficient information to assign a structure of (III). This, however, is not the case for (IV), since a similar ^{1}H NMR pattern should be observed for isomeric isoquinolinium compound having a six-membered heterocyclic ring. Therefore, an X-ray structural study of (IVa) was performed.

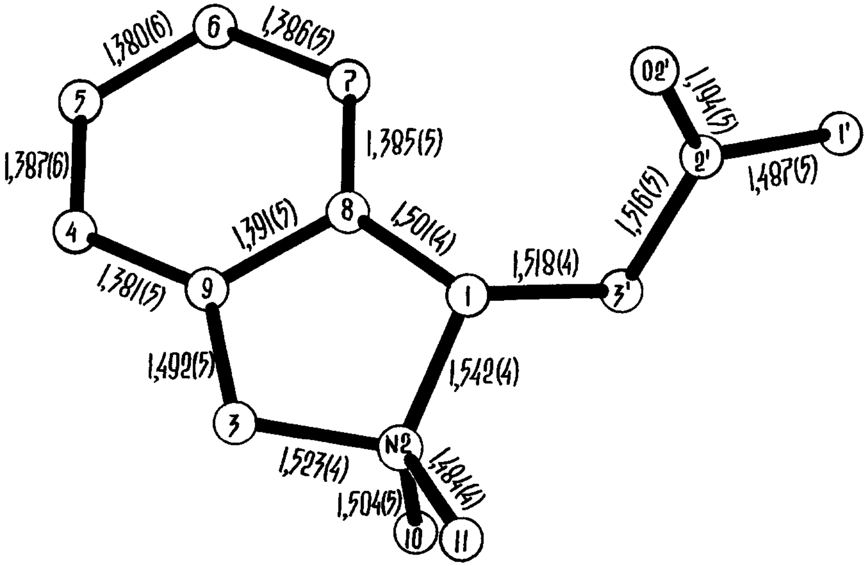
The structure[8] of the cation is presented below (the counter ion, tetrachloropalladate-(II) having a normal square planar configuration with a Pd-Cl bond length of 2.303(1) Å, is not shown). The cation involves the five-membered heterocycle in an envelope conformation, and (IVa) is thus [1-(propyl-2'-one)-2,2-dimethylisoindolinium] tetrachloropalladate(II). A similarity of spectral features of (IVa) and (IVb) suggests that the latter also contains the five-membered cycle and is thus [1-(propyl-2'-one)-2,2-dimethyl-5,6-dimethoxy-isoindolinium] hexachlorodipalladate(II).

The heterocyclic products (IV) are formed via an acid-promoted intramolecular amination of the primary products (II). Indeed, when acetic acid solutions of Li_2PdCl_4 are mixed with chloroform-acetic acid (1:1) solutions of (II) and allowed to stand at room temperature for 24 h, isoindolinium derivatives (IVa) or (IVb) are formed quantitatively.

Isoindoles, the chemistry of which has been intensively studied in recent years,[9] are not readily available compounds, thus, the approach put forward seems to be rather advantageous. Although intramolecular amination of alkenes is a long known procedure (see ref. 10 and the literature cited therein), its coupling with reactions involving palladocycles can open new horizons of the former.

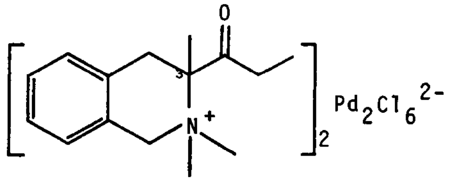
The cyclisation is a reversible process. On basification of (IV) with aqueous ammonia, for example, the isoindolinium ring undergoes Hoffmann cleavage to produce starting compounds (II).

We believe that palladium(II) is not directly involved in the cyclisation and serves as



a precipitating trap for the isoindolinium cations. It has been found by spectrophotometry that acidification of palladium free solutions of (IIa) by HCl leads to a dramatic decrease in absorption at 280 nm ($\epsilon = 15.9 \times 10^3$ dm^3 mol^{-1} cm^{-1}) to give a spectrum with a maximum at 270 nm ($\epsilon = 1.0 \times 10^3$ dm^3 mol^{-1} cm^{-1}) due to conversion of (IIa) into the isoindolinium cation with a loss of conjugation between arene, alkene, and carbonyl π-systems. Addition of base, on the other hand, restores the initial spectrum.

The cyclisation described here is typical of compounds with an activated double carbon-carbon bond only. When the acyl group in (II) is replaced by phenyl, the cyclisation does not occur and corresponding stilbenes have been isolated from acidic solutions as hydrochloride salts.[7a] At the same time the size of a heterocyclic ring formed depends on the nature of enone reacting with starting palladocycle (Ia). When 2-methyl-1-penten-3-one was used instead of 3-buten-2-one, in particular, the ^{1}H NMR spectrum of the heterocyclic product was consistent with structure (Va) having an isoquinoline skeleton.[11] A characteristic resonance from C^3-CH_3 protons appeared as a singlet, while a doublet should be expected if a five-membered ring were formed. We are currently investigating other alkenes in this reaction.



(Va)

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1. A. D. Ryabov, *Synthesis*, 1985, 233.
2. R. A. Holton, *Tetrahedron Lett.*, 1977, 355.
3. B. J. Brisdon, P. Nair, and S. F. Dyke, *Tetrahedron*, 1981, 37, 173.
4. (IIIa): Found: C 43.9, H 5.8, N 3.1, Cl 10.2%; calcd. for $C_{26}H_{32}N_2O_2Pd_2$: C 45.4, H 4.7, N 4.1, Cl 10.3%. Mp 180 °C (dec.). IR (KBr): 1610 and 1660 cm^{-1} (C=C, C=O). ^1H NMR (δ, $CDCl_3$-$d_5$pyridine): 7.49(d, J 16 Hz, ArCH=C), 7.24(d, J 8 Hz, H^3), 6.81(t, J 8 Hz, H^4), 6.55(d, J 16 Hz, C=CHCO), 6.05(d, J 8 Hz, H^5), 4.13(s, NCH_2), 2.88(s, NCH_3), 2.34(s, $COCH_3$).
5. (IVa): Found: C 46.7, H 5.5, N 4.2, Cl 21.7%; calcd. for $C_{26}H_{36}N_2O_2Cl_4Pd$: C 47.5, H 5.5, N 4.3, Cl 21.6%. Mp 179 °C (dec.). IR (KBr): 1720 cm^{-1} (C=O). ^1H NMR (δ, D_2O): 7.45 and 7.24(m, Ar), 5.40(J_{AX} 4.3, J_{BX} 8.1 Hz, C^1H), 3.61 and 3.40(J_{AB} 18.6 Hz, $COCH_2$), 3.36 and 3.04(s, NCH_3), 2.36(s, $COCH_3$); ($[CD_3]_2SO$): 4.92 and 4.81(d, J 7 Hz, C^3H_2).
6. (IVb): Found: C 36.8, H 4.9, N 3.8%; calcd. for $C_{30}H_{44}N_2O_6Cl_6Pd_2$: C 37.7, H 4.6, N 2.8%. Mp 162 °C (dec.). IR (KBr): 1705 (C=O). ^1H NMR (δ, D_2O): 7.07 and 6.82(s, Ar), 5.32(J_{AX} 4.8, J_{BX} 7.6 Hz, C^1H), 3.87 and 3.84(s, $ArOCH_3$), 3.60 and 3.36(J_{AB}19.0 Hz, $COCH_2$), 3.36 and 3.08(s, NCH_3), 2.34(s, $COCH_3$).
7. (a) A. D. Ryabov, V. A. Polyakov, and A. K. Yatsimirsky, *J. Chem. Soc., Perkin Trans. 2*, 1983, 1503; (b) A. D. Ryabov and A. K. Yatsimirsky, *Inorg. Chem.*, 1984, 23, 789.
8. Crystals of (IVa) are triclinic, space group $P\bar{1}$, a = 7.7867(6), b = 8.9834(6), c = 11.7100(8) Å, α = 97.984(5), β = 104.106(6), γ = 110.184(5)°, Z=1. 3243 Independent reflections were measured with an automatic four-circle Hilger-Watts diffractometer and 3207 of these with $F^2>3\sigma$ were used in a final refinement. The structure was solved by a heavy atom method. Hydrogen atoms were located from a difference map. The structure was refined by full-matrix least squares with anisotropic thermal factors for all nonhydrogen atoms. Positional parameters and B_{iso} of hydrogen atoms were fixed. The final discrepancy factors are R=0.0306, R_w=0.0366. Atomic coordinates are available on request from the Director of the Cambridge Crystallographic Centre, University, Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, England.
9. F. S. Babichev and V. A. Kovtunenko, *"Khimia Izoindola"* ("Isoindole Chemistry"), Naukova Dumka, Kiev, 1983 (Russ.).
10. A. J. Kirby and C. J. Logan, *J. Chem. Soc., Perkin Trans. 2*, 1978, 642.
11. (Va): Found: C 42.1, H 5.0, N 3.5%; calcd. for $C_{30}H_{44}N_2O_2Cl_6Pd_2$: C 40.5, H 4.9, N 3.2%. Mp 203-205 °C (dec.). IR (KBr): 1705 cm^{-1} (C=O). ^1H NMR (δ, D_2O): 7.70 and 7.44(m, Ar), 4.77(q, J 14 Hz, C^1H_2), 3.77(q, J 13 Hz, C^4H_2), 3.39 and 3.20(s, NCH_3), 2.90(s, C^3CH_3), 2.80(m, CH_2Me), 1.03(t, J 7 Hz, $CH_2\underline{CH_3}$).

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