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CYCLOPALLADATED IMINES IN SYNTHESIS 2[1]: A NEW SYNTHESIS OF ISOQUINOLINES

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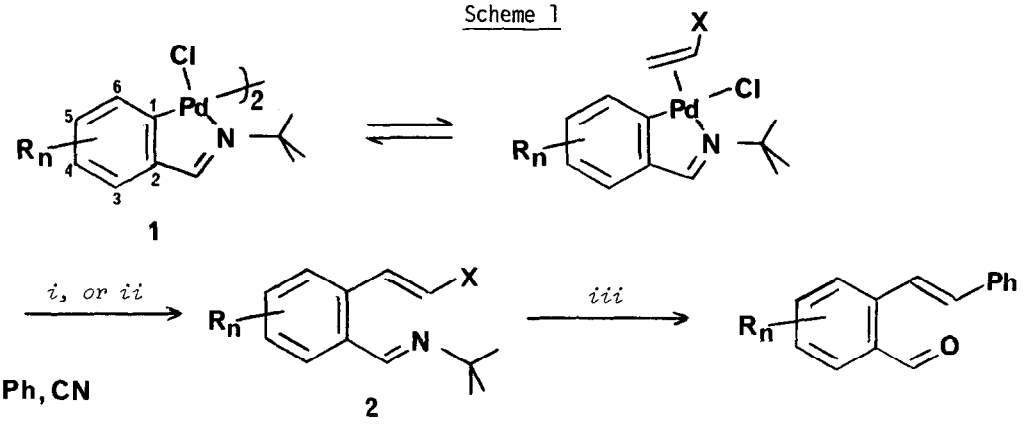
SUMMARY: *Reaction of cyclopalladated arylimines with acrylonitrile, followed by thermolysis gives isoquinolines by an electrocyclic ring forming process and a subsequent eliminative aromatisation step.*

Recently[1], we described the preparation of the complexes (1) and their reaction with styrene in acetic acid-trifluoroacetic acid to produce, after hydrolysis, 2-formylstilbenes (Scheme 1, X=Ph). These were converted, via the derived N-methylimines to N-methyl-3-phenylisoquinolines[2].

Scheme 1

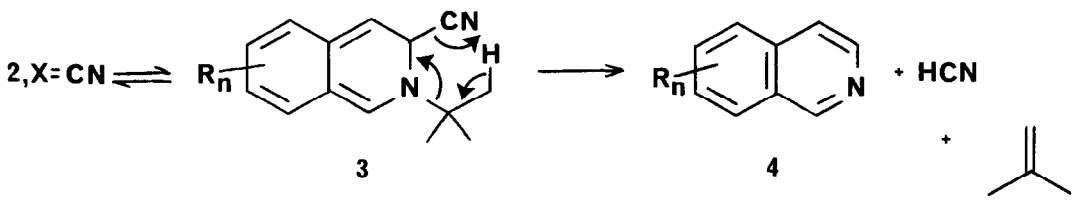


i, CH_2=CHPh/AcOH/TFA 5 → 25°; *ii*, CH_2=CHCN/Et_3N/PhMe, Δ; *iii*, H^+/H_2O, X = Ph

However, a more direct route to the isoquinoline ring system could be envisaged in which the imino-nitrogen was incorporated directly into the isoquinoline ring via an electrocyclic reaction (Scheme 2) which equilibrates the iminostyrene (2) with the closed form (3)[3]. Although the equilibrium would be expected to lie predominantly to the left, the overall transformation would be accomplished if in (2), X was a suitable leaving group which allowed an irreversible aromatisation step[4]. The insertion process of Scheme 1 is favoured by electron withdrawing groups X,[5] and the two requirements could be combined in the use of acrylonitrile (X = CN) as the initial substrate.

In the event, acrylonitrile inserted smoothly into the palladated imine (1, R = H) in the presence of triethylamine. The crude isolated imine (2, R = H) (78%) was heated to $\geq 160^{\circ}$ in an inert solvent (mesitylene) to generate isoquinoline in 24% overall yield.

Scheme 2



By using diphenyl ether/mesitylene (95:5) as solvent, the entire procedure could be carried out without isolation of the imines (2, X = CN). However, it was necessary to remove the volatile components, in vacuo and filter off the precipitated palladium and triethylamine hydrochloride before heating in the second stage.

A typical reaction procedure is: The complex (1) (0.015 mol)[†] was added to excess acrylonitrile (2 ml) and triethylamine (2 ml) in diphenylether/mesitylene (50 ml). The mixture was degassed and heated to $80\text{-}110^{\circ}$ under nitrogen during 8-12 h. The solids and volatiles were removed as described above and the solution heated to $180\text{-}200^{\circ}$ under nitrogen during 8-13 h. Work up for basic products (successive treatments: Et_2O, H_2O, aq. HCl, aq. Na_2CO_3) and flash chromatography over silica H60 (eluant ether-petroleum ether) gave the isoquinolines (Table).

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† *Complex (1, R_n = 5-Me) was not previously reported: Found, C, 45.53; H, 5.03; Cl, 11.41 N, 4.39. $C_{24}H_{32}Cl_2N_2Pd_2$ requires: C, 45.59; H, 5.1; Cl, 11.22; N, 4.43%; δ ($CDCl_3$) 1.51 (9H, s), 2.28 (3H, s), 7.0 (3H, m), and 7.76 (1H, s); δ ($CDCl_3$-d^5-pyridine) 1.64 (9H, s), 2.09 (3H, s), 5.7 (1H, m), 6.81 (1H, br d, J 7.5 Hz), 7.18 (1H, br d, J 7.5 Hz), and 7.88 (1H, s); ν_{max} (nujol) 1604 cm^{-1}.*

TABLE

Synthesis of Isoquinolines

Run	(1, R_n =)	STAGE 1 °C	STAGE 1 h	STAGE 2 °C	STAGE 2 h	(4, R_n =)[a]	(%)
1	H	110	9	190-5	13	H	(47)
2	5-Cl	110	8[b]	—		—	
3	5-Me	100	12	190	12	6-Me	(56)
4	5-MeO	110	8[b]	—		—	
5	4-MeO	110	12	200	8	7-MeO	(42)
6	3-MeO	95	14[b]	—		—	
7	4,5-$(MeO)_2$	100	12	180	8	6,7-$(MeO)_2$[c]	(10)

[a] *All isoquinoline products showed the expected spectral properties and/or m.p.'s which were identical with those reported in the literature.*[8]

[b] *These reactions were repeated with toluene as solvent and it was shown that insertion of acrylonitrile had not occurred.*

[c] *6,7-Dimethoxyisoquinoline was purified by chromatography on basic alumina H60.*

In contrast to the styrene insertions[1], these acrylonitrile reactions show a pronounced substituent effect which is readily explained if an initial equilibrium complexation of the olefin is followed by a rate determining insertion reaction. This reaction is expected to be facilitated by an increase in the positive character of the palladium atom[6] and here shows some of the characteristics of an electrophilic aromatic substitution[7]. Thus a π-donor substituent p- to palladium (Table, Runs 5,7) allows ready insertion but when o- or p- to the imine function (Table, Runs 2, 4, 6), inhibits insertion by lowering the positive character of the palladium. Remote inductive effects (Table, Run 3) do not significantly change the reaction[7].

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REFERENCES

1. Part 1, I.R. Girling and D.A. Widdowson, Tetrahedron Letters, 1982, 1957.

2. For a general account of transition metals in heterocyclic synthesis, see: J.D. Davidson and P.N. Preston, Adv. Heterocyclic Chem., 1982, 30, 319; R.C. Larock, Heterocycles, 1982, 18, 397.

3. C.W. Spangler, Chem. Rev., 1976, 76, 187.

4. The aromatisation process may be concerted. For similar processes, see: G.G. Smith and F.W. Kelly, Progr. in Phys. Org. Chem., 1971, 8, 75; J.B. Hendricksen, Angew. Chem. Int. Ed., 1974, 13, 47; M. Rosenblum, A. Lonroy, M. Neveu, and C. Steel, J. Am. Chem. Soc., 1965, 87, 5716.

5. R.F. Heck, Acc. Chem. Res., 1979, 12, 146. H. Horino and N. Inoue, J. Org. Chem., 1981, 46, 4416; R.A. Holton, Tetrahedron Letters, 1977, 355; S.F. Dyke and M.J. McCartney, Tetrahedron, 1981, 37, 431; Y. Fujiwara, O. Maruyama, M.Yoshidomi and H. Taniguchi, J. Org. Chem., 1981, 46, 851.

6. cf. D.J. Mabbott and P.M. Maitlis, J. Organomet. Chem., 1975, 102, C34; H.C. Clark, and H. Kurosawa, J.C.S. Chem. Commun., 1971, 957; ibid., Inorg. Chem., 1972, 11, 1275; A.J. Deeming, B.F.G. Johnson, and J. Lewis, J.C.S. Chem. Commun., 1970, 598.

7. cf. R.A. Holton and K.J. Natalie, Tetrahedron Letters, 1981, 267.

8. Isoquinoline: Aldrich catalogue of N.M.R. Spectra, 9, 114D; 6-Methylisoquinoline: C. Pomerantz, Monatsch., 1897, 18, 1; 7-Methoxyisoquinoline: P. Fritsch, Annalen, 1895, 286, 1; 6,7-Dimethoxyisoquinoline: F.D. Popp and W.E. McEwen, J. Am. Chem. Soc., 1957, 79, 3773.

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