Journal of Organometallic Chemistry, 397 (1990) C31–C32
Elsevier Sequoia S.A., Lausanne

JOM 21287PC

Preliminary communication

A new palladium-catalyzed synthesis of indoxyl derivatives

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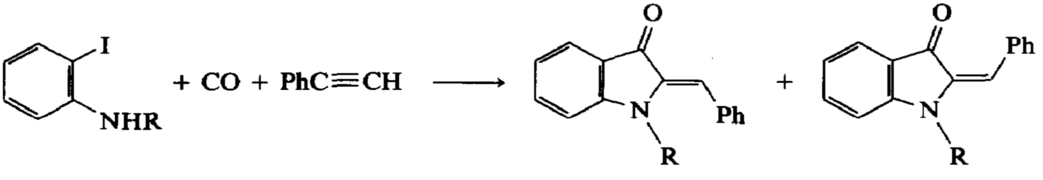
(Received July 20th, 1990)

Abstract

The reaction of iodoanilines with phenylacetylene and carbon monoxide catalyzed by a palladium(0) catalyst leads to indoxyl derivatives.

Benzylidene derivatives of indoxyl are interesting prototypes of indigoid dyes [1]. They are generally made starting from indoxyl and aldehydes [2], and application of organometallic chemistry in their synthesis has not been previously reported. Related stoichiometric cyclizations of 2-allylanilines to 2-methylindoles [3], of 2-bromoacetanilides and ethylene to indoles [4] and of 2′-aminocalchones to 2-aryl-4-quinolones [5] have been described. It is noteworthy that the latter reaction did not give any benzylidene derivative of indoxyl.

We now describe a simple palladium(0)-catalyzed synthesis of **I**, starting from iodoaniline or its derivatives (R = H or hydrocarbyl), carbon monoxide and phenylacetylene (eq. 1):



(I*Z*) (I*E*)

(1)

The reaction goes surprisingly well even with the simplest reagent *o*-iodoaniline, which might be expected to cause catalyst inhibition. Thus stirring of equimolecular amounts of iodoaniline, phenylacetylene, and potassium acetate with 0.04 mol of $Pd(PPh_3)_4$ per mole of iodoaniline in anisole under atmospheric pressure of carbon monoxide at 80 °C for 23 h resulted in a 92% yield of **I** and its precursor, 2′-aminophenyl-3-phenyl-2-propyn-1-one, **II** (84 : 16 molar ratio, 66 : 34 at 75% conversion).

0022-328X/90/$03.50

Compound **I** (R = H) was obtained exclusively in the *Z* form [1]. This is also the preferred form for aurone [6]. However, when a substituent such as the acetyl group is present on nitrogen, steric hindrance plays an important role in giving rise to the presence of the *E* product alongside the *Z* isomer. The *E* form of *I* (R = MeCO) initially predominates (*Z* : *E* molar ratio = 1 : 2 at 73% conversion), but higher ratios (2 : 1) are found at complete conversion. Separation of the reaction mixture by TLC afforded a 93% yield. This means that the amination reaction (from **II** to **I**) first gives the kinetically controlled product *E*, and the subsequent isomerization is sufficiently slow to allow isolation of the latter in higher amount than that present at the thermodynamic equilibrium. That equilibrium has been found to lie between a 2 : 1 and 3 : 1 *Z* : *E* molar ratio by inducing the *Z* product to isomerize under the same reaction conditions.

The possibility of exerting a steric influence on an amination reaction to obtain a majority of *Z* or *E* isomers offers interesting mechanistic aspects as well as synthetic potential.

Some properties of products **I** (R = MeCO), *Z* and *E*, and **II** are given below.

Compound I (R = MeCO, *Z* form): yellow crystals, m.p. (acetone, 5 ° C) 132–133 ° C; MS (70 eV): M^+ 263, *m/e* 262, 221, 220, 219, 204, 191, 190, 165, 164, 90, 89, 76, 63, 50; IR (film): 1715, 1700, 1645 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, TMS): δ 8.27 (1H, H4, dt, *J* 8.3, 0.7 Hz), 7.83 (1H, H7, ddd, *J* 7.6, 1.4, 0.7 Hz), 7.65 (1H, H5, ddd, *J* 8.3, 8.2, 1.4 Hz), 7.58–7.34 (5H, phenyl group), 7.32 (1H, =C–H), 7.28 (1H, H6, td partially obscured, *J* 7.5, 0.9 Hz), 1.94 (3H, OCH_3).

Compound I (R = MeCO, *E* form): yellow crystals, m.p. (ethyl ether) 90–91 ° C; MS (70 eV): the same pattern as for the *Z* form; IR (film): 1710 (shoulder), 1695, 1625 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, TMS): δ 8.10 (1H, H4, dt, *J* 8.4, 0.8 Hz), 7.89–7.80 (2H, phenyl, m), 7.75 (1H, H7, ddd, *J* 7.5, 1.5, 0.7 Hz), 7.61 (1H, H5, ddd, *J* 8.4, *J* 1.5 Hz), 7.54 (1H, =C–H, s), 7.46–7.37 (3H, phenyl, m), 7.23 (1H, H6, td, *J* 7.5, 0.8 Hz), 2.62 (3H, CH_3, s).

Compound II: MS (70 eV): M^+ 221, *m/e* 220, 204, 193, 165, 129, 119, 92; IR (film): 3450, 3340, 2210, 1630, 1595 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, TMS): δ 8.16 (1H, H6′, dd, *J* 8.1, 1.7 Hz), 7.68–7.60 (2H, H2, H6, m), 7.48–7.37 (3H, H3, H4, H5, m), 7.30 (1H, H4′, ddd, *J* 8.2, 7.0, 1.6 Hz), 6.70 (1H, H5′, ddd partially overlapped, *J* 8.1, 7.0, 1.1 Hz), 6.64 (1H, H3′, dd partially overlapped, *J* 8.1, 1.1 Hz), 6.37 (2H, NH_2, brs).

Acknowledgement. Z.A. (on leave from Modern Chemistry Research Institute, Xian, China) was recipient of a grant from the Third World Academy of Sciences, Trieste. We thank Ministero Ricerca Scientifica and Progetto Finalizzato Chimica Fine 2 for financial support and Centro Interfacoltà di Misure of the University of Parma for NMR and MS facilities.

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