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PALLADIUM-CATALYSED COUPLING OF ARYL AND VINYL TRIFLATES OR HALIDES WITH 2-ETHYNYLANILINE: AN EFFICIENT ROUTE TO FUNCTIONALIZED 2-SUBSTITUTED INDOLES

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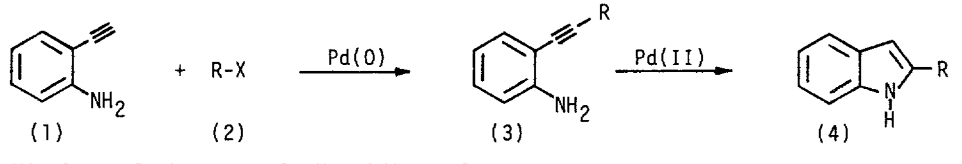
Summary - The palladium(0)-catalysed coupling of aryl and vinyl triflates or halides with the easily available 2-ethynylaniline, followed by a palladium(II)-catalysed cyclization step, provides an efficient and very versatile procedure for the synthesis of functionalyzed 2-substituted indoles.

In recent years, considerable attention has been directed towards the use of transition metals in developing synthetic methods for the building up of the indole nucleus,[1] a structural subunit common to a wide variety of biologically active products. A simple way to gain this end is based on transition metals[1c,2,3] and base[4] catalysed cyclization of 2-alkynyl and 2-arylethynylanilines (anilides). These compounds were prepared by treating 2-thallated-N-acylanilides with phenylethynylcopper,[3] coupling of 2-iodoaniline with alkynylcopper reagents,[2] coupling of 2-bromo-N-carbonylanilide with 1-alkynes in the presence of Pd(0),[4] and reacting N-benzyl-N-trimethylsililoxy anilines with trialkynylaluminium.[5] However, these procedures require stoichiometric amounts of organometallic intermediates,[2,3] elevated temperatures,[2] protection of the amino group,[1c,3,4] reagents and/or reaction conditions[4,5] unable to tolerate a large number of functionalities. Furthermore, they all need preformed 1-alkynes. Perhaps because of these disadvantages, these reactions have not been widely employed. Only simple 2-substituted indoles have been prepared by using these methodologies and the scope of the palladium-catalysed cyclization of 2-alkynylanilines has not been really investigated.

Since recent reports from our laboratories and others showed that a variety of 1-alkynes could react with vinyl[6] and aryl[7] triflates to give 1-vinylated and 1-arylated alkynes and the procedure appeared expecially promising as a method for the synthesis of 2-alkynyl- and 2-(arylethynyl)anilines containing complex functionalyzed moieties, we attempted to develop a new and more versatile procedure to 2-substituted indoles based on the utilization of the easily available 2-ethynylaniline (1) as the starting building block.



R = Vinyl, aryl, heteroaryl; X = OTf, I, Br

Scheme 1

Herein we report that this method provides a general, high-yield route for the synthesis of functionalyzed 2-substituted indoles (see Table). The reaction conditions are mild and compatible with a variety of functional groups elsewhere in the molecule.

Table - Synthesis of 2-Alkynyl-/2-Arylethynylanilines (3) and 2-Substituted Indoles (4).

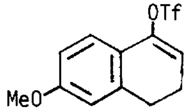
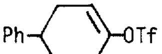
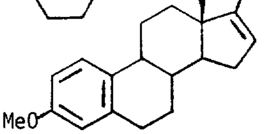
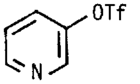
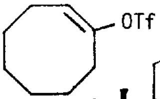
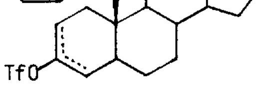
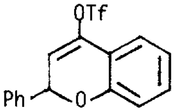
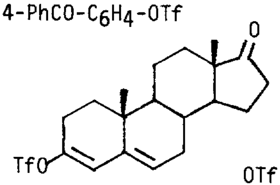
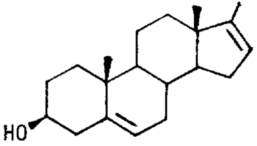
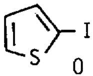
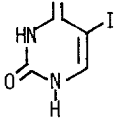
Entry	Vinyl/aryl triflate or halide (2)	2-Alkynyl/2-Arylethynyl anilines (3) yield %[a,b] (reaction time)	2-Substituted indoles (4) yield %[a,h] (reaction time)
a		91 (5 h)	64 (3.5 h)
b		67 (4 h)	87 (3 h)
c		94 (5 h)	75 (4 h)[i]
d	2-naphthyl-triflate	85 (3 h)	76 (3.5 h)
e f g		28 (5 h) 59 (5 h)[c] 67 (5 h)[d]	38 (36 h) 21 (8 h)[l]
h		95 (4 h)	80 (9 h)
i		98 (4 h)	77 (4 h)[m]
l		55 (3 h)	60 (4 h)
m n	4-Me-C_6H_4-OTf "	-- (4 h)[c] 95 (4.5 h)[d]	 80 (3 h)
o	4-PhCO-C_6H_4-OTf	85 (1 h)[d]	39 (3 h)
p		90 (4 h)	82 (4.5 h)[n]
q		86 (4 h)[f]	64 (4 h)[o]
r	3-F-C_6H_4-I	80 (4 h)	51 (6 h)
s	PhCH=CHBr[p]	81 (4 h)	74 (2.5 h)

Table - Synthesis of 2-Alkynyl-/2-Arylethynylanilines (3) and 2-Substituted Indoles (4).

Entry	Vinyl/aryl triflate or halide (2)	2-Alkynyl/2-Arylethynyl anilines (3) yield % ^{a,b} (reaction time)	2-Substituted indoles (4) yield % ^{a,h} (reaction time)
t		80 (6 h)	82 (3 h)
u		90 (8 h)^g	28 (4.5 h)^q

a) Yields are for pure, isolated products. Reaction conditions are not optimized. All compounds had satisfactory elemental analysis and spectral data were consistant with postulated structures. b) Carried out at room temperature by using the following molar ratios: (1):(2):$Pd(PPh_3)_4$:CuI:Et_2NH = 1:1:0.01:0.02:20, unless otherwise specified. c) LiCl (300 mol %) was added. d) Carried out at 90°C in DMF by using the following molar ratios: (1):(2):$PdCl_2(PPh_3)_2$:Et_3N = 1:1.4:0.03:4. e) Obtained from the corresponding 3-keto derivative and reacted as a mixture of isomeric Δ^2- and Δ^3-3-triflates. f) The starting triflate contains the 3-ß-trifluoroacetoxy group which decomposes to 3-ß-hydroxy group under reaction conditions. g) Carried out in a Et_2NH/H_2O 2/1 mixture; (1):Et_2NH:H_2O = 2.3 mmol:8 ml:4 ml. h) Carried out at 70°C in MeCN by using the following molar ratios: (3):$PdCl_2$ = = 1:0.05. i) (3):MeCN = 0.68 mmol:80 ml. l) Carried out at 100°C in DMF. m) (3):MeCN = 0.44 mmol:40 ml. n) (3):MeCN = 0.35 mmol:20 ml. o) (3):MeCN = 0.39 mmol:40 ml. p) A commercially available E/Z mixture was used but, according to the literature data,[8] the E isomer was found to react preferentially. q) Carried out at 120°C in DMF; the starting material was recovered in 22% yield.

2-Ethynylaniline (1) was prepared through a straighforward palladium-catalysed coupling of 2-iodoaniline with ethynyltrimethylsilane[9] followed by desililation with KF[10] in 81% overall yield.

$$2\text{-}H_2N\text{-}C_6H_4\text{-}I \quad + \quad HC{\equiv}C\text{-}SiMe_3 \quad \xrightarrow[\text{2) } KF\cdot 2H_2O\text{, MeOH, r.t.}]{\text{1) } Pd(PPh_3)_4\text{, CuI, } Et_2NH\text{, r.t.}} \quad (1)$$

Scheme 2

Palladium-catalysed coupling of (1) with aryl and vinyl triflates [$Pd(PPh_3)_4$, CuI, Et_2NH, room temperature, 3-5 h] affords 2-alkynyl- and 2-arylethynylanilines (3) usually in high yield. With aryltriflates, the addition of an excess of LiCl,[11] reported to act as a ligand exchanger in the initially-formed organopalladium triflates, may improve the yields (entry f). However, the presence of LiCl not always meets with success (entry m). Better results are in these cases obtained by treating compounds (2) with $PdCl_2(PPh_3)_2$ in Et_3N at 90°C for 1-5 h omitting CuI (entries g, n, o).[7]

$PdCl_2$[3,12] has been proved to be an efficient catalyst for cyclization of (3) to 2-substituted indoles (4) with a variety of systems we examined. Only 2-arylethynylanilines containing electron-withdrawing groups near or conjugated with the acetylenic triple bond produced the indole derivative in moderate yield (compare, for example, entry n with o and r).

Compounds (4) were prepared from aryl and vinyl halides as well (entries r-u).

Currently, we are applying this procedure to the synthesis of other heterocyclic systems.

Preparation of 2-ethynylaniline (1): To a stirred solution of 2-iodoaniline (2.995 g, 13.7 mmol) and diethylamine (10 ml) in DMF (2 ml), are added ethynyltrimethylsilane (2.84 ml, 20.5 mmol), $Pd(PPh_3)_4$ (78 mg, 0.07 mmol), and CuI (27 mg, 0.14 mmol). The reaction mixture is stirred at room temperature for 6 h under nitrogen. Diethylether and 0.1 N HCl are added and the organic layer is separated, neutralized with a saturated $NaHCO_3$ solution, washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. The residue is dissolved in 60 ml of MeOH, $KF \cdot 2H_2O$ (3.89 g, 41 mmol) is added and the mixture is stirred for 7 h at room temperature. Diethyl ether and water are added and, after work-up, flash chromatography of the residue (silica gel, 92/8 hexane/ethyl acetate) affords (1) (1.29 g, 81% yield); as an oil; IR (liquid film) 3440, 3340, 3250, 2070, 1600, 740 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 7.5-7.03 (m,2H), 6.83-6.53 (m,2H), 4.18 (bs,2H), 3.37 (s,1H).

Typical procedure for the synthesis of 2-substituted indoles (4): A mixture of 2-ethynylaniline (0.22 g, 1.9 mmol), 3,4-dihydro-6-methoxy-1-naphthyl triflate (2a) (0.59 g, 1.9 mmol), $Pd(PPh_3)_4$ (21 mg, 0.019 mmol), CuI (7.2 mg, 0.038 mmol), and diethylamine (4 ml) in DMF (1 ml) is stirred at room temperature for 5.5 h under nitrogen. After usual work-up, the crude product is purified by flash chromatography (silica gel , 90/10 hexane/ethyl acetate) to give (3a) (0.47 g, 91% yield); m.p. 58-61°C; IR (liquid film) 3460, 3360, 2190 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 7.8-6.6 (m,7H), 6.43 (m,1H), 4.23 (m,2H), 3.79 (s,2H), 3.0-2.67 (m,2H), 2.6-2.23 (m,2H).

A mixture of compound (3a) (0.4 g, 1.45 mmol) and $PdCl_2$ (13 mg, 0.072 mmol) in MeCN (10 ml) is stirred at 75°C for 3.5 h under nitrogen. After solvent removal under reduced pressure, the residue is purified by flash chromatography (silica gel, 90/10 hexane ethyl acetate) to give (4a) (0.23 g, 64% yield); m.p. 121-123°C; IR (KBr) 3360 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 8.13 (bs,1H), 7.8-6.53 (m,7H), 6.23 (m,1H), 3.81 (s,3H), 2.97-2.67 (m,2H), 2.53-2.2 (m,2H); MS(m/e): 275 (M^+), 260.

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