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ORIGINAL ARTICLE

Ultrasound assisted Mizoroki–Heck reaction catalyzed by Pd/C: Synthesis of 3-vinyl indoles as potential cytotoxic agents

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Abstract The Pd/C–PPh_3 catalyst system facilitated the C–C bond forming reaction between 3-iodo-1-methyl-1*H*-indole and various terminal alkenes under ultrasound irradiation. The present ultrasound assisted Mizoroki–Heck coupling afforded a number of 3-vinyl indole derivatives in good to acceptable yields. Two of these indole derivatives showed cytotoxic activities against breast cancer cell lines.

1. Introduction

The indole ring is considered as one of the privileged frameworks in medicinal and pharmaceutical chemistry. For example, 3-substituted indole nucleus is prevalent in numerous natural products and is extremely important in medicinal chemistry (Sharma et al., 2010; Carbone et al., 2013a,b). Indeed, 3-vinyl indole derivatives have been used as precursors (Zheng et al., 2015; Zhang et al., 2014; Zheng et al., 2014) for several bioactive agents that include the total synthesis of (±)-aplicyanins A, B and E and related analogues several of which showed considerable cytotoxicity (Šíša et al., 2009). The (*E*)-6-fluoro-3-[2-(3-pyridyl)vinyl]-1*H*-indole (**A**, Fig. 1) has been identified as a novel inhibitor of tryptophan 2,3-dioxygenase (TDO) thereby potential anticancer immunomodulator (Salter et al., 1995). Similarly, (*E*)-3-(2-carboxy-2-phenylvinyl)-4,6-dichloro-1*H*-indole-2-carboxylic acid (**B**, Fig. 1) has been identified as a potent and selective antagonist of the glycine site of the *N*-methyl-d-aspartate (NMDA) receptor (Baron et al., 2005). Very recently, 3-vinyl indole derivatives (**C**, Fig. 1) have been reported as inhibitors of diacylglycerol acyltransferase-1 (Kim et al., 2015) and *trans*-indole-3-acrylamide derivatives have been reported as a new class of tubulin polymerization inhibitors (Baytas et al., 2014).

The 3-vinyl indole derivatives are generally prepared from the corresponding aldehydes by using Horner–Wadsworth–Emmons olefination or similar methods (Šíša et al., 2009; Su et al., 2014; Lopez-Alvarado et al., 2009; Sodeoka et al., 2003; Pindur et al., 1989, 1995;

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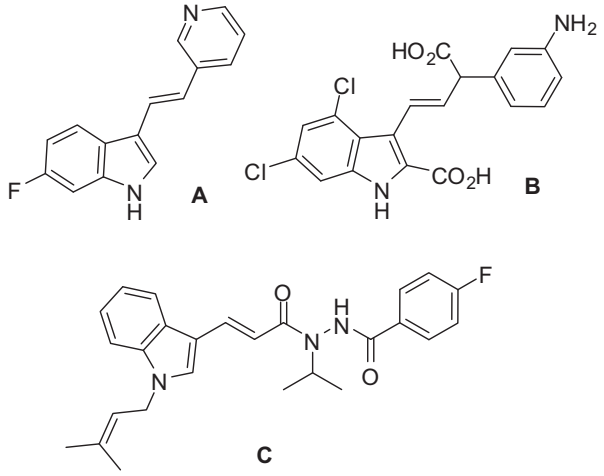


Figure 1 Examples of bioactive 3-vinyl indole derivatives.

Pindur and Pfeuffer, 1989). While being effective these methods however involve the cumbersome preparation of required organophosphorus reagents and removal of phosphorus containing by-product from the desired product. The methodology based on Pd-catalyzed coupling of an aryl/vinyl halide with an alkene, popularly known as Mizoroki–Heck reaction (Mizoroki et al., 1971; Heck, 1982; Tsuji, 1995; Beccalli et al., 2010; Farina, 2004; Cabri and Candiani, 1999; Beccalli et al., 2006) has been extended (Harrington and Hegedus, 1984; Harrington et al., 1987; Gribble and Conway, 1992) for the preparation of 3-vinyl indole derivatives (Sala et al., 2006). The use of 3-iodoindoles possessing an electron withdrawing group on the indole nitrogen was found to be more effective than the corresponding 3-bromoindoles in these coupling reactions. The use of C–H activation strategy has been explored for the preparation of 3-vinyl indoles (Sala et al., 2006; Fujiwara et al., 1981; Itahara et al., 1983, 1984; Capito et al., 2005; Grimster et al., 2005; Yokoyama et al., 1995; Osanai et al., 1999; Djakovitch and Rouge, 2007, 2009; Chen et al., 2012; Huang et al., 2013). Very recently, an elegant Pd(II)-catalyzed triple successive oxidative Heck (Fujiwara–Moritani reaction) of indole has been reported (Verma et al., 2015). While the direct use of indole in place of expensive 3-haloindoles is the major advantage of these methodologies, the requirement of excess quantity of Pd-catalyst and/or oxidants, low conversion rate along with C-2 vs C-3 selectivity in addition to the use of sealed tube [or oxygen pressure (1 atmosphere) (Chen et al., 2012)] is the practical drawbacks in several cases. Notably, the aerobic *dehydrogenative Heck reaction* (DHR) of heterocycles with styrenes has been reported to be more efficient in the absence of metallic co-oxidants (Vasseur et al., 2013). Nevertheless, due to our continuing interest in bioactive indole derivatives (Pal et al., 2004a,b; Rao et al., 2011; Nakhi et al., 2011; Kumar et al., 2012; Gorja et al., 2013; Dulla et al., 2014) we required a more convenient and direct access to a library of 3-vinyl indoles for our in house pharmacological screen.

The use of Pd/C in Mizoroki–Heck reaction has been reported earlier (Hagiwara et al., 2001; Xie et al., 2004; Perosa et al., 2004; Köhler et al., 2002; Köhler et al., 2008). Being less expensive, stable, easy to handle and recyclable catalyst Pd/C has advantages over the other Pd-complexes or salts. Indeed, the combination of Pd/C with ionic liquid as a recyclable catalyst system for the Mizoroki–Heck coupling has been documented in the literature (Hagiwara et al., 2001; Perosa et al., 2004). Moreover, these reactions can be accelerated when performed under microwave irradiation (Perosa et al., 2004). The Mizoroki–Heck reaction (Deshmukh et al., 2001; Zhang et al., 2006; Palmisano et al., 2007; Garella et al., 2010; An et al., 2011; Yahiaoui et al., 2011) of iodobenzene with methyl acrylate has also been studied using Pd/C as a catalyst in the presence of ultrasound (Ambulgekar et al., 2005). Like microwave, ultrasound enhanced the reaction rate as expected and was found to be essential for the reaction to proceed at room temperature. While the effects of base, solvent and recyclability of catalyst were studied in the presence and absence of ultrasound, the application and scope of this ultrasound based methodology in organic synthesis has not been explored. Only one and simple example was studied in this case. It was therefore necessary to examine the utility of this strategy as a general and greener method for the C–C bond forming reaction. Herein we report Pd/C mediated Mizoroki–Heck coupling of 3-iodoindole (**1**) with various alkenes (**2**) under ultrasound irradiation leading to 3-vinyl indoles (**3**) (Scheme 1). Notably, preparation of this class of indole derivatives using ultrasound assisted Mizoroki–Heck reaction catalyzed by Pd/C is not known (Cacchi and Fabrizi, 2005; Broggini et al., 2012; Clique et al., 2003).

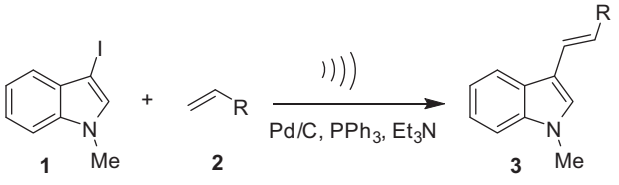
2. Materials and methods

2.1. General methods

Unless stated otherwise, reactions were performed under nitrogen atmosphere using oven-dried glassware. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light or iodine spray. Flash chromatography was performed on silica gel (230–400 mesh) using distilled hexane and ethyl acetate. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 solution by using 400 or 100 MHz spectrometers, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, $\delta = 0.00$) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), dd (doublet of doublet), td (triplet of doublet), t (triplet) and m (multiplet) as well as b (broad). Coupling constants (J) are given in hertz. MS spectra were obtained on a Agilent 6430 series Triple Quard LC-MS/MS spectrometer. Melting points (mp) were recorded by using Buchi B-540 melting point apparatus and are uncorrected. A laboratory ultrasonic bath SONOREX SUPER RK 510H model producing irradiation of 35 kHz was used for performing reactions under ultrasound irradiation.

2.2. Preparation 3-iodo-1-methyl-1H-indole (*1*) (Bocchi et al., 1982)

To a stirring solution of 1-methyl indole (2.0 mmol) in DMF (10 mL) was added a solution of iodine (2.05 mmol) in DMF (10 mL) dropwise at 25–30 °C. Stirring continued at the same temperature till completion of the reaction (indicated by TLC). Then the reaction mixture was poured into cold water (250 mL) containing sodium thiosulphate (10%). The solid separated was filtered, washed with cold water (10–15 °C), dried and recrystallized from 5% to 10% hexane/EtOAc (1 mL for 50 mg) to give the desired product in 90% yield;



Scheme 1 Synthesis of 3-vinyl indoles via ultrasound assisted Mizoroki–Heck reaction catalyzed by Pd/C.

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yellow solid; mp 56–58 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (dd, J = 8.0 and 0.7 Hz, 1H), 7.38–7.30 (m, 3H), 7.08 (s, 1H), 3.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.4, 132.4, 130.1, 122.4, 120.8, 120.0, 109.2, 54.5, 32.8.

2.3. General procedure for the preparation of 3-vinyl indoles (**3**) (Bocchi et al., 1982)

A mixture of substituted indole **1** (0.3 mmol, 1.0 equiv.), alkene **2** (0.36 mmol, 1.2 equiv.), 10% Pd/C (0.05 equiv.), PPh_3 (0.10 equiv.), and Et_3N (0.6 mmol, 2.0 equiv.) in DMF (5.0 mL) was stirred at 30 °C under ultrasound (using a laboratory ultrasonic bath SONOREX SUPER RK 510H model producing irradiation of 35 kHz) in the presence of nitrogen atmosphere. After completion of the reaction (indicated by TLC) the mixture was diluted with cold water (30 mL), and extracted with EtOAc (3 × 30 mL). The combined organic phases were collected, washed with cold brine solution (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using 2–5% hexane-EtOAc (TLC $R_f \sim 0.5$) as eluant to give the desired product.

2.3.1. (*E*)-Butyl-3-(1-methyl-1H-indol-3-yl)acrylate (**3a**) (Chen et al., 2012)

Light yellow solid; 62–64 °C; IR (neat) ν: 3054, 1704, 1627 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89–7.84 (m, 2H), 7.30–7.21 (m, 4H), 6.41 (d, J = 15.7 Hz, 1H), 4.20 (t, J = 6.2 Hz, 2H), 3.72 (s, 3H), 1.71–1.65 (m, 2H), 1.46–1.41 (m, 2H), 0.97 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 137.8, 137.8, 133.0, 125.8, 122.7, 121.1, 120.4, 112.4, 112.0, 109.8, 63.8, 33.0, 30.8, 19.1, 13.6; HRMS (ESI) calcd for $C_{16}H_{19}NO_2Na$ [M + Na$^+$]: 280.1308, found: 280.1310.

2.3.2. (*E*)-tert-Butyl 3-(1-methyl-1H-indol-3-yl)acrylate (**3b**) (Tao et al., 2014)

Yellow low melting solid; IR (neat) ν: 3057, 1705, 1625 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, J = 7.8 Hz, 1H), 7.77 (d, J = 15.6 Hz, 1H), 7.30–7.20 (m, 4H), 6.34 (d, J = 15.6 Hz, 1H), 3.73 (s, 3H), 1.54 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 137.8, 136.8, 132.7, 126.0, 122.7, 121.0, 120.4, 114.4, 112.1, 109.8, 79.5, 33.0, 28.2; HRMS (ESI) calcd for $C_{16}H_{19}NO_2Na$ [M + Na$^+$]: 280.1308, found: 280.1311.

2.3.3. (*E*)-Methyl-2-(1-methylindol-3-yl)acrylate (**3c**) (Pindur et al., 1989)

Light brown solid, mp 95–97 °C; IR (neat) ν: 3055, 1706, 1629 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93–7.87 (m, 2H), 7.36–7.23 (m, 4H), 6.41 (d, J = 15.7 Hz, 1H), 3.82 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 138.1, 138.0, 133.0, 126.0, 122.8, 121.2, 120.4, 112.1, 112.0, 109.8, 51.2, 33.1; HRMS (ESI) Calcd for $C_{13}H_{13}NO_2$ [M$^+$]: 215.0946, found: 215.0949.

2.3.4. (*E*)-Ethyl-3-(1-methyl-1H-indol-3-yl)acrylate (**3d**) (Chen et al., 2012)

Yellow solid; mp 95–98 °C; IR (neat) ν: 3053, 1704, 1613 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.76 (m, 2H), 7.22–7.15 (m, 4H), 6.33–6.30 (d, J = 15.8 Hz, 1H), 4.19–4.14 (q, J = 6.6 Hz, 2H), 3.65 (s, 3H), 1.27–1.23 (t, J = 7.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 138.0, 133.2, 126.0, 122.9, 121.3, 120.6, 112.5, 112.0, 109.9, 60.1, 33.1, 14.5; HRMS (ESI) Calcd for $C_{14}H_{15}NO_2$ [M$^+$]: 229.1103, found: 215.1109.

2.3.5. (*E*)-1-Methyl-3-styryl-1H-indole (**3e**) (Chen et al., 2012)

Off white solid; mp 96–98 °C; IR (neat) ν: 3052, 1632, 1514 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 8.02 (d, J = 7.5 Hz, 1H), 7.54 (d, J = 7.5 Hz, 2H), 7.41–7.22 (m, 8H), 7.12 (d, J = 16.3 Hz, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.6, 137.6, 128.5, 128.4, 126.3, 126.0, 125.6, 124.6, 122.1, 121.5, 120.1, 120.0, 114.0, 109.5, 32.8; HRMS (ESI) calcd for $C_{17}H_{16}N$ [M + H$^+$]: 234.1277, found: 234.1273.

2.3.6. (*E*)-N,N-dimethyl-3-(1-methyl-1H-indol-3-yl)acrylamide (**3f**)

Pale yellow solid; mp 97–99 °C; IR (neat) ν: 3054, 1654, 1510 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90–7.85 (m, 2H), 7.33–7.20 (m, 4H), 6.85 (d, J = 15.3 Hz, 1H), 3.76 (s, 3H), 3.15–3.10 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 137.8, 135.7, 132.4, 126.0, 122.5, 120.7, 120.3, 112.5, 111.8, 109.8, 37.2, 35.8, 33.0; HRMS (ESI) calcd for $C_{14}H_{17}N_2O$ [M + H$^+$]: 229.1335, found: 229.1332.

2.3.7. (*E*)-N,N-diethyl-3-(1-methyl-1H-indol-3-yl)acrylamide (**3g**) (Chen et al., 2012)

Light brown solid; mp 94–96 °C; IR (neat) ν: 3055, 1655, 1514 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 15.8 Hz, 1H), 7.84 (d, J = 7.9 Hz, 1H), 7.31–7.22 (m, 4H), 6.80 (d, J = 15.8 Hz, 1H), 3.73 (s, 3H), 3.50–3.48 (m, 4H), 1.28–1.18 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 137.9, 135.6, 132.4, 126.0, 122.6, 120.8, 120.2, 112.6, 112.2, 109.9, 42.2, 41.0, 33.0, 15.0, 13.4; HRMS (ESI) calcd for $C_{16}H_{20}N_2O$ [M + Na$^+$]: 279.1468. Found: 279.1465.

2.3.8. (*E*)-1-(1-methyl-1H-indol-3-yl)oct-1-en-3-one (**3h**)

Light brown low melting solid; IR (neat) ν: 3055, 2356, 1705, 1514 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, J = 7.6 Hz, 1H), 7.77 (d, J = 15.7 Hz, 1H), 7.31–7.22 (m, 4H), 6.74 (d, J = 15.7 Hz, 1H), 3.75 (s, 3H), 2.60 (t, J = 7.3 Hz, 2H), 1.70 (t, J = 7.3 Hz, 2H), 1.36–1.31 (m, 4H), 0.90 (t, J = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.7, 138.0, 135.8, 133.6, 126.0, 123.0, 121.3, 121.2, 120.4, 112.0, 110.0, 40.7, 33.0, 31.5, 24.4, 22.4, 13.8; HRMS (ESI) calcd for $C_{17}H_{22}NO$ [M + H$^+$]: 256.1696, found: 256.1698.

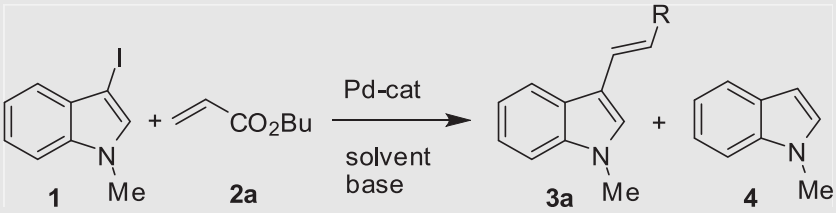
2.3.9. (*E*)-4-(1-methyl-1H-indol-3-yl)but-3-en-2-one (**3i**) (Caballero et al., 2001)

Yellow low melting solid; IR (neat) ν: 3058, 2360, 1707, 1516, 1129 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 7.7 Hz, 1H), 7.75 (d, J = 16.0 Hz, 1H), 7.38–7.26 (m, 4H), 6.75 (d, J = 16.0 Hz, 1H), 3.81 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.4, 138.1, 137.0, 133.5, 126.0, 123.0, 122.3, 121.3, 120.5, 112.0, 110.0, 33.1, 27.2; HRMS (ESI) calcd for $C_{13}H_{14}NO$ [M + H$^+$] 200.1075, found: 200.1077.

2.3.10. (*E*)-3-(1-methyl-1H-indol-3-yl)-1-phenylprop-2-en-1-one (**3j**) (Order et al., 1945; Black et al., 1992)

Yellow solid; mp 96–98 °C; IR (neat) ν: 3089, 2365, 1741, 1516 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10–8.01

Table 1 Effect of reaction conditions on the coupling of **1** with **2a**.[a]



Entry	Catalyst	Solvent/base	Temp (°C)/time (h)	% yield[b]	
				3a	**4**
1.	$(PPh_3)_2PdCl_2$	Et_3N	90/6	49	21
2.	$Pd(OAc)_2$–PPh_3	Et_3N	90/6	47	20
3.	$Pd(OAc)_2$–PPh_3	DMF/Et_3N	100/6	50	17
4.	10%Pd/C–PPh_3	DMF/Et_3N	100/12	43	27
5.	10%Pd/C–PPh_3	DMF/Et_3N	50/2	78[c]	11
6.	10%Pd/C–PPh_3	DMF/Et_3N	30/2	75[c]	10
7.	PPh_3	DMF/Et_3N	30/12	0[c,d]	0
8.	10%Pd/C	DMF/Et_3N	30/12	Trace[c,e]	0
9.	10%Pd/C–PPh_3	DMF/K_2CO_3	30/12	19[c]	0
10.	10%Pd/C–PPh_3	EtOH/Et_3N	30/12	10[c]	66

[a] All reactions were carried out using **1** (1 equiv.), alkene **2a** (1.2 equiv.), a Pd-catalyst (0.05 equiv.), PPh_3 (0.10 equiv.) where necessary and a base (2 equiv.) in a solvent (5.0 mL) (5 mL of Et_3N was used as a base as well as solvent in case of entries 1 and 2) under nitrogen.
[b] Isolated yield.
[c] The reaction was carried out under ultrasound irradiation.
[d] The reaction was carried out without Pd/C.
[e] The reaction was carried out without PPh_3.

(m, 4H), 7.58–7.46 (m, 5H), 7.38–7.30 (m, 3H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6, 139.0, 138.5, 138.2, 134.5, 132.0, 128.4, 128.2, 126.0, 123.1, 121.5, 120.7, 117.0, 113.0, 110.1, 33.2; HRMS (ESI) calcd for $C_{18}H_{16}NO$ [M + H^+] 262.1232, found: 262.1228.

2.3.11. (*E*)-3-(1-methyl-1*H*-indol-3-yl)acrylonitrile (**3k**) (Chen et al., 2012; López et al., 2005)

Light brown solid; mp 92–94 °C; IR (neat) *v*: 3052, 2145, 1515 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 7.9 Hz, 1H), 7.46 (d, J = 15.9 Hz, 1H), 7.35–7.25 (m, 4H), 5.70 (d, J = 15.9 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 138.0, 133.1, 125.4, 123.4, 121.8, 120.2, 120.1, 111.8, 110.3, 89.3, 33.3; HRMS (ESI) calcd for $C_{12}H_{11}N_2$ [M + H^+] 183.0922, found: 183.0925.

2.4. Sulforhodamine B (SRB) assay

Cancer cells (around 5000 in number) were seeded in 96-well plates and incubated overnight. The optimum cell number to be seeded was determined by a growth curve analysis for the cell line. Compounds (dissolved in 100% DMSO to a stock concentration of 200 mM) were added to the adhered cells at a final concentration of 10 μM. After 72 h of treatment, the cells were washed with phosphate-buffered saline and ice-cold 10% trichloroacetic acid was added to the cells to precipitate the proteins. It was incubated for 1 h at 4 °C. The cells were then washed with water and air-dried. Cellular proteins were then stained using 0.4% SRB solution in 1% acetic acid for 30 min at room temperature (25 °C). The unbound dye was washed away by destaining with 1% acetic acid and bound dye was solubilized with 10 mM Tris solution (pH 10.5). Absorbance of solubilized dye was measured at a wavelength of 590 nm. Percentage growth was determined by the formula

$$[(At - A0/Ac - A0)] \times 100$$

where At = absorbance after 72 h of test compound treatment, $A0$ = absorbance at time 0, Ac = absorbance after 72 h without treatment.

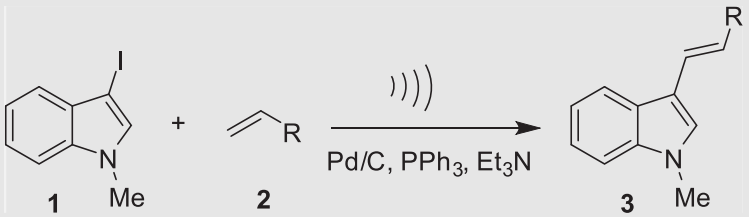
The known cytotoxic agent, gemcitabine was used as a positive control in the assay.

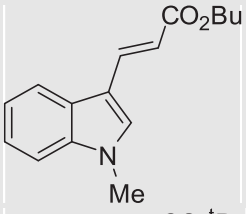
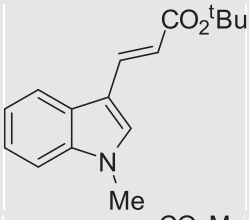
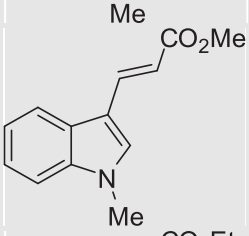
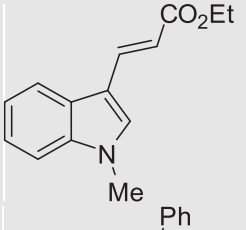
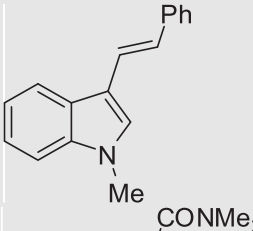
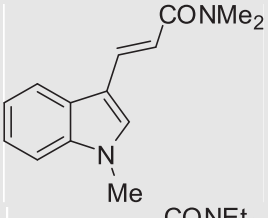
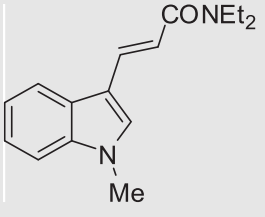
3. Results and discussion

3.1. Chemistry

We began our study with the coupling reaction of 3-iodo-1-methyl-1*H*-indole (**1**), prepared according to a known procedure (Bocchi and Palla, 1982), with n-butyl acrylate (**2a**) under standard Mizoroki–Heck reaction conditions. The use of conventional palladium catalytic systems e.g. $(PPh_3)_2PdCl_2$ or $Pd(OAc)_2$–PPh_3 did not afford the good yield of desired product **3a** (entries 1–2, Table 1). The dehalogenated product **4** was also isolated as a side product (20–21% yield) in these cases. These reactions were carried out at 90 °C using Et_3N as a base as well as solvent. The use of a high boiling solvent such as DMF though allowed the reaction to proceed at higher temperature no significant change in the yield of **3a** and **4** was observed (entry 3, Table 1). The change of catalyst to 10% Pd/C–PPh_3 and use of longer reaction time also did not change the ratio of **3a** and **4** formed (entry 4, Table 1). Notably, a significant improvement in yield of **3a** was observed when the

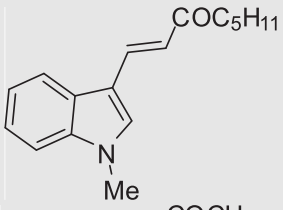
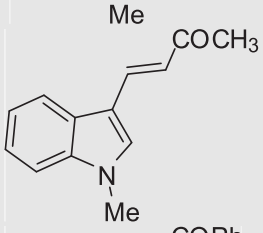
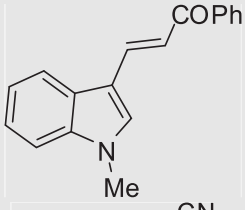
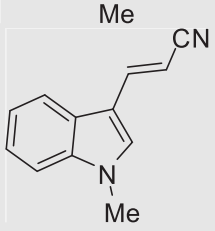
Table 2 Preparation of 3-vinyl indoles via ultrasound assisted Mizoroki–Heck reaction catalyzed by Pd/C.[a]



Entry	Alkene (**2**); R =	Time (h)	Product (**3**)	% yield[b]
1.	**2a**; $-CO_2Bu$	2	**3a**; 	75
2.	**2b**; $-CO_2^tBu$	2	**3b**; 	77
3.	**2c**; $-CO_2Me$	3	**3c**; 	71
4.	**2d**; $-CO_2Et$	2.5	**3d**; 	73
5.	**2e**; –Ph	2	**3e**; 	70
6.	**2f**; $-CONMe_2$	2.5	**3f**; 	72
7.	**2g**; $-CONEt_2$	2.5	**3g**; 	73

(*continued on next page*)

Table 2 (*continued*)

Entry	Alkene (**2**); R =	Time (h)	Product (**3**)	% yield[b]
8.	**2h**; $-COC_5H_{11}$	3	**3h**; 	69
9.	**2i**; $-COCH_3$	3	**3i**; 	65
10.	**2j**; –COPh	2.5	**3j**; 	75
11.	**2k**; –CN	2	**3k**; 	78
12.	**2l**; $-CH_2OC_2H_5$		–	0
13.	**2m**; (*E*)-ethyl but-2-enoate		–	0

[a] All reactions were carried out using **1** (1 equiv.), alkene **2** (1.2 equiv.), 10%Pd/C (0.05 equiv.), PPh_3 (0.10 equiv.) and Et_3N (2 equiv.) in DMF (5.0 mL) at 30 °C under nitrogen.
[b] Isolated yield.

reaction was performed under ultrasound irradiation (using a laboratory ultrasonic bath SONOREX SUPER RK 510H model producing irradiation of 35 kHz) instead of conventional heating (entry 5, Table 1). Indeed, the reaction proceeded at lower temperature (50 °C) and reached to the completion within 2 h as indicated by thin layer chromatography (TLC). A further decrease in reaction temperature to 30 °C did not affect the product yield (entry 6, Table 1). While the side reaction involving dehalogenation of **1** was not suppressed completely in these cases we were delighted to achieve the higher yield of **3a**. To assess the role of catalyst, ligand and base in the present 3-alkenylation of indole the coupling reaction was performed in the absence of Pd/C (entry 7, Table 1), PPh_3 (entry 8, Table 1) and K_2CO_3 in place of Et_3N (entry 9, Table 1) separately. The reaction either did not proceed or afforded poor yield of **3a** in these cases. All these observations clearly indicated the key role played by the Pd/C, PPh_3 and Et_3N in the present reaction whereas the use of ultrasound allowed a faster reaction at a lower temperature with improved yield of **3a**. The change of solvent from DMF to EtOH was also examined when the dehalogenated product **4** was obtained as a major product. Overall, the condition of entry 6 appeared as the best for synthesizing **3a** and was used for further study.

A number of 3-vinyl indole derivatives (**3a–i**) were prepared using the optimized reaction conditions (Table 2). A variety of terminal alkenes (**2a–i**) generally bearing an electron withdrawing groups such as ester, amide, ketone, aryl and cyano moiety were employed in the present coupling reaction (entries 1–11, Table 2). The reaction proceeded well in all these cases affording the corresponding desired product in acceptable yields. Notably, terminal alkenes that do not possess an electron withdrawing group (entry 12, Table 2) or alkenes possessing substituent at both ends [e.g. (*E*)-ethyl but-2-enoate) (entry 13, Table 2) were found to be less reactive in the present coupling reaction. The use of acrolein was also not successful due to its quick polymerization under the condition studied. We also examined the use of 3-iodo-1-(phenylsulfonyl)-1*H*-indole in place of 3-iodo-1-methyl-1*H*-indole (**1**) that was treated with **2a** under the optimized condition (entry 6, Table 1). However, the reaction afforded a mixture of product with poor yield of the desired indole derivative. Though a marginally better yield of desired product was obtained when 3-bromo-1-methyl-1*H*-indole was employed the reaction also afforded appreciable quantity of dehalogenated product (i.e. 1-methyl-1*H*-indole) as a by-product. Nevertheless, all the 3-vinyl indole derivatives (**3a–i**) synthesized were characterized by spectral data. The

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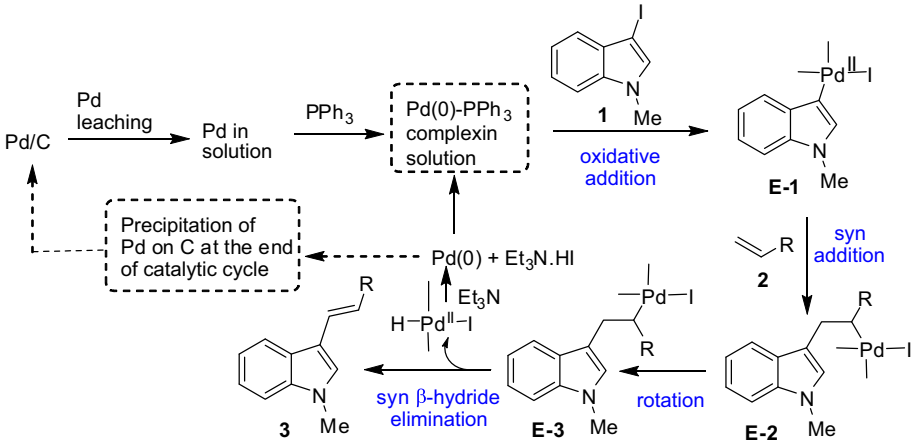

Scheme 2 Probable mechanism of Pd/C-catalyzed coupling of **1** with alkene **2**.

E-geometry of the double bond was confirmed by the coupling constant (*J*) of olefinic protons of all the compounds that were found to be ~16 Hz. It is worthy to mention that 3-vinyl indole derivatives e.g. compound **3b** have been used for the construction of benzo[*a*]carbazole-5-carboxylates *via* the Diels–Alder reaction (Tao et al., 2014). Thus the synthetic utility of 3-vinyl-indoles has been demonstrated via their uses in Diels–Alder chemistry as a route to carbazoles and related species (Pindur and Otto, 1992; Lambert and Porter, 1981; Pindur et al., 1992; Tan et al., 2011; Cowell et al., 2015; Gioia et al., 2008).

A plausible reaction mechanism for the present Pd/C-catalyzed coupling of **1** with **2** under ultrasound is presented in Scheme 2. The reaction involves *in situ* generation of an active palladium(0) species (Pal, 2009; Rambabu et al., 2013; Chen et al., 2007) *via* a Pd leaching process from the minor portion of the bound palladium (Pd/C) (Köhler et al., 2002) and then goes into the solution. The leached Pd then undergoes interaction with PPh_3 to give a dissolved Pd(0)–PPh_3 complex. Notably the generation of active species from supported Pd catalyst under Heck reaction conditions has been studied earlier (Reimann et al., 2011). Nevertheless, being the actual catalytic species this complex then participates in oxidative addition with **1** to give the organo-palladium(II) species **E-1**. Subsequent formation of a π-complex of **E-1** with the alkene **2** (not shown) followed by syn addition of Pd-carbon bond of **E-1** across the double bond of **2** affords **E-2**. A torsional strain relieving rotation around the C–C bond of **E-2** gives **E-3** which then undergoes a *syn* β-hydride elimination to give the product **3** and $HPd^{II}I$ species. The regeneration of Pd(0) via reductive elimination of Pd from $HPd^{II}I$ species completes the catalytic cycle which continues till the complete consumption of **1**. Overall, the catalytic cycle appears to operate in solution instead of on the surface and re-precipitation of Pd occurs on the surface of the charcoal at the end of the reaction.

The results of Table 1 clearly suggest that the Pd/C-catalyzed coupling reaction was facilitated when performed under ultrasound irradiation though it is not clear whether the ultrasound has effect on one or more steps as shown in Scheme 2. It is known that the presence of an electron donating group on the indole nitrogen generally is not favorable for coupling at C-3 perhaps due to the high electron density of the iodo group bearing carbon resulting in a slower oxidative addition of Pd(0) to **1** (Scheme 2). The ultrasound possibly provides a positive effect on this step with the force created due to the cavitational collapse. Indeed, the cavitational collapse creates drastic conditions inside the medium within an extremely short period of time, e.g. the temperature of 2000–5000 K and pressure up to 1800 atmosphere can be produced inside the collapsing cavity under sonic conditions (Suslick and Flannigan, 2008; Mason, 1997; Luche, 1998). Also, strong physical effects including shear forces, jets, and shock waves are caused by this collapse outside the bubble. Thus, it is possible that the oxidative addition step (along with several other steps) was particularly driven by the force created due to the cavitational collapse. It is also possible that the Pd leaching process thereby *in situ* generation of active Pd(0) species was accelerated by the ultrasound. Notably, the ultrasound may facilitate the generation of Pd(0) nanoparticles that may serve as a reservoir of "homogeneous" catalytic active species (Cassol et al., 2005). The role of Pd nanoparticles in Heck and other coupling reactions (e.g. Suzuki–Miyaura reaction) has been studied (Ellis et al., 2010; Baumann et al., 2014).

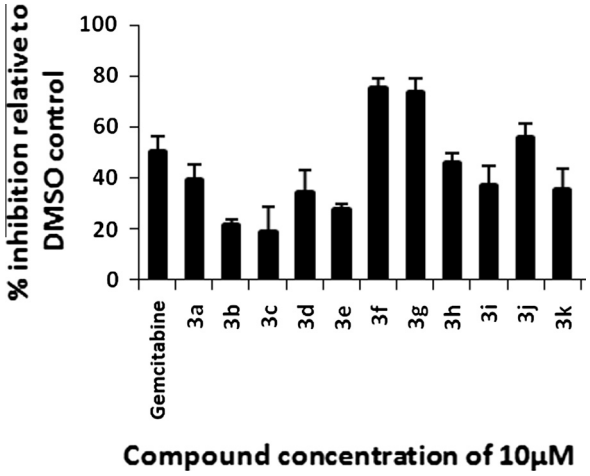

Figure 2 % Inhibition of breast adenocarcinoma cells (MCF-7) after 72 h of compound treatment.

3.2. Pharmacology

Due to the known anticancer properties of various 3-substituted indole derivatives all the synthesized compounds

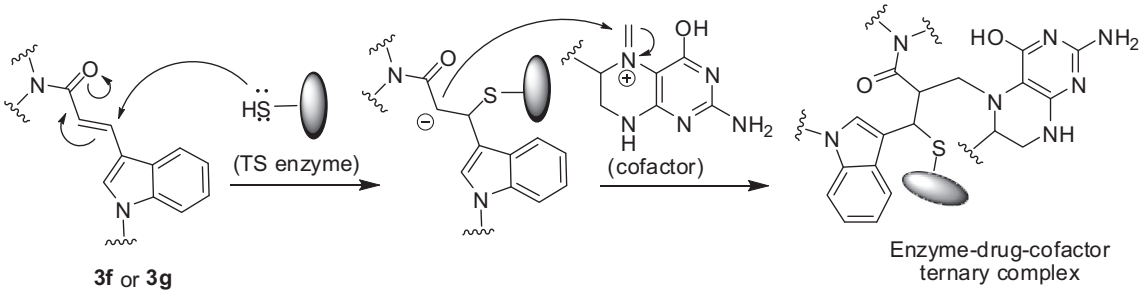

Figure 3 Possible interactions of compounds **3f** and **3g** with TS enzyme.

were evaluated for their ability to inhibit the growth of cancer cells. These compounds were tested at 10 μM against three cancer cells e.g. A549 (lung), MCF-7 (breast) and TZM-BL (cervical) using the sulforhodamine B (SRB) assay (Rubinstein et al., 1990; Skehan et al., 1990) with gemcitabine (Chu and DeVita, 2007) as a reference compound. Except **3f** and **3g** all these compounds showed moderate to weak activities against the lung, breast and cervical cancer cells. However, the compounds **3f** and **3g** showed >75% inhibition against breast cancer (MCF-7) cells (comparable to gemcitabine's ~ 50% inhibition) (Fig. 2) though they were found to be less active against other two cancer cells. Moreover, these compounds did not show significant effect on normal HEK 293T cells (10–15% inhibition vs gemcitabine's 25%) indicating their selectivity toward cancer cells. Notably, comparison of structural features of compounds **3f** and **3g** with other indicates that the presence of an amide (–$CONMe_2$ or –$CONEt_2$) moiety could be responsible for their cytotoxic activities against MCF-7 cells. A possible explanation for observed cytotoxic activities of **3f** and **3g** could be their potential inhibition of thymidilate synthase (TS), a key enzyme required for cellular growth (Rao et al., 1998). Like 5-fluorouracil, the enone moiety (of **3f** and **3g**) may facilitate the binding of TS enzyme (Papamichael, 1999; Kundu et al., 1993) through its sulfhydryl (–SH) moiety with compounds **3f** and **3g** in the presence of cofactor methylene tetrahydrofolate thereby generating the corresponding enzyme-drug-cofactor complexes (Fig. 3). However, the low or moderate activities shown by other compounds in spite of the presence of enone moiety were not clearly understood. The participation of amide nitrogen (i.e. a mild H-bond acceptor) of **3f** and **3g** in additional interactions with the TS enzyme or cofactor could be the other reason. It is also not clear why these two compounds showed low activities against other cancer (e.g. lung and cervical) cell lines. Nevertheless, the observed selectivity of compounds **3f** and **3g** toward breast cancer cells is interesting. Thus, the present study indicated that the indole ring possessing an acrylamide moiety at C-3 could be a potential template for the identification of new anticancer agents.

5. Conclusion

In conclusion, the Pd/C–PPh_3 catalyst system has been found to be effective in facilitating the C–C bond forming reaction between 3-iodo-1-methyl-1*H*-indole and various terminal alkenes under ultrasound irradiation. A variety of terminal alkenes containing an ester, amide, ketone and aryl moiety were employed in this ultrasound assisted Mizoroki–Heck reaction. The reaction proceeded well in all these cases affording the corresponding 3-vinyl indole derivatives in good to acceptable yields. The advantages and drawbacks along with the reaction mechanism of this methodology are discussed. All indole derivatives synthesized were tested against three cancer cell lines including lung, breast and cervical cancer. Two of these indole derivatives showed cytotoxic activities against breast cancer cells. Overall, the Pd/C based methodology presented here could be useful for the quicker access to a library of compounds based on 3-vinyl indole framework of potential pharmacological interest.

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References

Ambulgekar, G.V., Bhanage, B.M., Samant, S.D., 2005. Low temperature recyclable catalyst for Heck reactions using ultrasound. Tetrahedron Lett. 46, 2483–2485.

An, G., Ji, X., Han, J., Pan, Y., 2011. Ultrasound-promoted ligand-free heck reaction in water. Synth. Commun. 41, 1464–1471.

Baron, B.M., Cregge, R.J., Farr, R.A., Friedrich, D., Gross, R.S., Harrison, B.L., Janowick, D.A., Matthews, D., McCloskey, T.C., Meikrantz, S., Nyce, P.L., Vaz, R., Metz, W.A., 2005. CoMFA, synthesis, and pharmacological evaluation of (E)-3-(2-carboxy-2-arylvinyl)-4,6-dichloro-1H-indole-2-carboxylic acids: 3-[2-(3-aminophenyl)-2-carboxyvinyl]-4,6-dichloro-1H-indole-2-carboxylic acid, a potent selective glycine-site NMDA receptor antagonist. J. Med. Chem. 48, 995–1018.

Bocchi, V., Palla, G., 1982. High yield selective bromination and iodination of indoles in *N*,*N*-dimethylformamide. Synthesis, 1096–1097.

Baytas, S.N., Inceler, N., Yılmaz, A., Olgac, A., Menevse, S., Banoglu, E., Hamel, E., Bortolozzi, R., Viola, G., 2014. Synthesis, biological evaluation and molecular docking studies of *trans*-indole-3-acrylamide derivatives, a new class of tubulin polymerization inhibitors. Bioorg. Med. Chem. 22, 3096–3104.

Baumann, C.G., De Ornellas, S., Reeds, J.P., Storr, T.E., Williams, T. J., Fairlamb, I.J.S., 2014. Formation and propagation of well-defined Pd nanoparticles (PdNPs) during C–H bond functionalization of heteroarenes: are nanoparticles a moribund form of Pd or an active catalytic species? Tetrahedron 70, 6174–6187.

Beccalli, Egle M., Borsini, E., Brenna, S., Galli, S., Rigamonti, M., Broggini, G., 2010. σ-Alkylpalladium intermediates in intramolecular heck reactions: isolation and catalytic activity. Chem. Eur. J. 16, 1670–1678.

Broggini, G., Beccalli, E.M., Fasana, A., Gazzola, S., 2012. Palladium-catalyzed dual C–H or N–H functionalization of unfunctionalized indole derivatives with alkenes and arenes. Beilstein J. Org. Chem. 8, 1730–1746.

Beccalli, E.M., Broggini, G., Martinelli, M., Masciocchi, N., Sottocornola, S., 2006. New 4-spiroannulated tetrahydroisoquinolines by a one-pot sequential procedure. isolation and characterization of σ-alkylpalladium heck intermediates. Org. Lett. 8, 4521–4524.

Black, D.S., Debdas, R.B., Kumar, N., 1992. Nitrones and oxaziridines. XLII. Synthesis of indol-3-yl-substituted 1-pyrroline 1-oxides. Aust. J. Chem. 45, 611–621.

Capito, E., Brown, J.M., Ricci, A., 2005. Directed palladation: fine tuning permits the catalytic 2-alkenylation of indoles. Chem. Commun., 1954–1956

Chen, W.-L., Gao, Y.-R., Mao, S., Zhang, Y.-L., Wang, Y.-F., Wang, Y.-Q., 2012. Palladium-catalyzed intermolecular C3 alkenylation of indoles using oxygen as the oxidant. Org. Lett. 14, 5920–5923.

Chen, J.-S., Vasiliev, A.N., Panarello, A.P., Khinast, J.G., 2007. Pd-leaching and Pd-removal in Pd/C-catalyzed Suzuki couplings. Appl. Catal., A Gen. 325, 76–86.

Cacchi, S., Fabrizi, G., 2005. Synthesis and functionalization of indoles through palladium-catalyzed reactions. Chem. Rev. 105, 2873–2920.

Carbone, A., Parrino, B., Barraja, P., Spanò, V., Cirrincione, G., Diana, P., Maier, A., Kelter, G., Fiebig, H.-H., 2013a. Synthesis and antiproliferative activity of 2,5-bis(3′-indolyl)pyrroles, analogues of the marine alkaloid nortopsentin. Mar. Drugs 11, 643–654.

Carbone, A., Pennati, M., Parrino, B., Lopergolo, A., Barraja, P., Montalbano, A., Spanò, V., Sbarra, S., Doldi, V., De Cesare, M., Cirrincione, G., Diana, P., Zaffaroni, N., 2013b. Novel 1*H*-pyrrolo [2,3-*b*]pyridine derivative nortopsentin analogues: synthesis and antitumor activity in peritoneal mesothelioma experimental models. J. Med. Chem. 56, 7060–7072.

Cabri, W., Candiani, I., 1999. Recent developments and new perspectives in the Heck reaction. Acc. Chem. Res. 28, 2–7.

Caballero, E., Longieras, N., Zausa, E., del Rey, B., Medarde, M., Tomé, F., 2001. Diels–Alder reactivity and some synthetic applications of (E)-1-(3-indolyl)-3-tert-butyldimethylsiloxy-1,3-butadienes. Tetrahedron Lett. 42, 7233–7236.

Cassol, C.C., Umpierre, A.P., Machado, G., Wolke, S.I., Dupont, J., 2005. The role of Pd nanoparticles in ionic liquid in the Heck reaction. J. Am. Chem. Soc. 127, 3298–3299.

Cowell, J., Abualnaja, M., Morton, S., Linder, R., Buckingham, F., Waddell, P.G., Probert, M.R., Hall, M.J., 2015. Diastereoselective synthesis of functionalised carbazoles *via* a sequential Diels–Alder/ene reaction strategy. RSC Adv. 5, 16125–16152.

Clique, B., Fabritius, C.-H., Couturier, C., Monteiro, N., Balme, G., 2003. Unexpected isolation, and structural characterization, of a β-hydrogen-containing σ-alkylpalladium halide complex in the course of an intramolecular Heck reaction. Synthesis of polycyclic isoquinoline derivatives. Chem. Commun., 272–273

Chu, E., DeVita, V.T., 2007. Physicians' Cancer Chemotherapy Drug Manual. Jones & Bartlett.

Dulla, B., Sailaja, E., Reddy CH, U., Aeluri, M., Kalle, A.M., Bhavani, S., Rambabu, D., Rao, M.V.B., Pal, M., 2014. Synthesis of indole based novel small molecules: their *in vitro* anti-proliferative effects on various cancer cell lines. Tetrahedron Lett. 55, 921–926.

Deshmukh, R.R., Rajagopal, R., Srinivasan, K.V., 2001. Ultrasound promoted C–C bond formation: Heck reaction at ambient conditions in room temperature ionic liquids. Chem. Commun., 1544–1545

Djakovitch, L., Rouge, P., 2007. New homogeneously and heterogeneously [Pd/Cu]-catalysed C3-alkenylation of free NH-indoles. J. Mol. Catal. A: Chem. 273, 230–239.

Djakovitch, L., Rouge, P., 2009. Environmentally friendly [Pd/Cu]-catalysed C3-alkenylation of free NH-indoles. Catal. Today 140, 90–99.

Ellis, P.J., Fairlamb, I.J.S., Hackett, S.F.J., Wilson, K., Lee, A.F., 2010. Evidence for the surface-catalyzed Suzuki-Miyaura reaction over palladium nanoparticles: an operando XAS study. Angew. Chem. Int. Ed. 49, 1820–1824.

Fujiwara, Y., Maruyama, O., Yoshidomi, M., Taniguchi, H., 1981. Palladium-catalyzed alkenylation of aromatic heterocycles with olefins. Synthesis of functionalized aromatic heterocycles. J. Org. Chem. 46, 851–855.

Farina, V., 2004. High-turnover palladium catalysts in cross-coupling and Heck chemistry: a critical overview. Adv. Synth. Catal. 346, 1553–1582.

Gribble, G.W., Conway, S.C., 1992. Palladium-catalyzed coupling of 3-indolyl triflate. Synthesis of 3-vinyl and 3-alkynylindoles. Synth. Commun. 22, 2129–2141.

Grimster, N.P., Gauntlett, C., Godfrey, C.R.A., Gaunt, M.J., 2005. Palladium-catalyzed intermolecular alkenylation of indoles by solvent-controlled regioselective C–H functionalization. Angew. Chem. Int. Ed. 44, 3125–3129.

Gorja, D.R., Mukherjee, S., Meda, C.L.T., Deora, G.S., Kumar, K.L., Jain, A., Chaudhari, G.H., Chennubhotla, K.S., Banote, R.K., Kulkarni, P., Parsa, K.V.L., Mukkanti, K., Pal, M., 2013. Novel *N*-indolylmethyl substituted olanzapine derivatives: their design, synthesis and evaluation as PDE4B inhibitors. Org. Biomol. Chem. 11, 2075–2079.

Garella, D., Tagliapietra, S., Mehta, V., Van der Eycken, E., Cravotto, G., 2010. Straightforward functionalization of 3,5-dichloro-2-pyrazinones under simultaneous microwave and ultrasound irradiation. Synthesis, 136–140.

Gioia, C., Hauville, A., Bernardi, L., Fini, F., Ricci, A., 2008. Organocatalytic asymmetric Diels–Alder reactions of 3-vinylindoles. Angew. Chem., Int. Ed. 47, 9236–9239.

Heck, R.F., 1982. Palladium-catalyzed vinylation of organic halides. Org. React. 27, 345–390.

Harrington, P.J., Hegedus, L.S., 1984. Palladium-catalyzed reactions in the synthesis of 3- and 4-substituted indoles. Approaches to ergot alkaloids. J. Org. Chem. 49, 2657–2662.

Harrington, P.J., Hegedus, L.S., McDaniel, K.F., 1987. Palladium-catalyzed reactions in the synthesis of 3- and 4-substituted indoles. 2. Total synthesis of the N-acetyl methyl ester of (.+−.)-clavicipitic acids. J. Am. Chem. Soc. 109, 4335–4338.

Hagiwara, H., Shimizu, Y., Hoshi, T., Suzuki, T., Ando, M., Ohkubo, K., Yokoyama, C., 2001. Heterogeneous Heck reaction catalyzed by Pd/C in ionic liquid. Tetrahedron Lett. 42, 4349–4351.

Huang, Q., Song, Q., Cai, J., Zhang, X., Lin, S., 2013. Palladium(II)/polyoxometalate-catalyzed direct c-3 alkenylation of indoles using dioxygen as the terminal oxidant. Adv. Synth. Catal. 355, 1512–1516.

Itahara, T., Ikeda, M., Sakakibara, T., 1983. Alkenylation of 1-acylindoles with olefins bearing electron-withdrawing substituents and palladium acetate. J. Chem. Soc., Perkin Trans. 1, 1361–1363.

Itahara, T., Kawasaki, K., Ousetu, F., 1984. Alkenylation of 1-benzenesulfonylation with olefins bearing electron-withdrawing substituents. Synthesis, 236–237.

Kim, M., Kwon, J., Kim, M.O., Singh, S., Kim, S.K., Lee, K., Lee, K., Lee, H.S., Choi, Y., 2015. Discovery of a novel series of indolyl hydrazide derivatives as diacylglycerol acyltransferase-1 inhibitors. Bull. Korean Chem. Soc. 36, 628–635.

Kumar, K.S., Kumar, P.M., Rao, V.S., Jafar, A.A., Meda, C.L.T., Kapavarapu, R., Parsa, K.V.L., Pal, M., 2012. A new cascade reaction: concurrent construction of six and five membered ring leading to novel fused quinazolinones. Org. Biomol. Chem. 10, 3098–3103.

Kundu, N.G., Dasgupta, S., Chaudhuri, L.N., Mahanty, J.S., S.H., 1993. Synthesis and biological activities of [E]-5-(2-acylvinyl) uracils. Eur. J. Med. Chem. 28, 473–479.

Köhler, K., Heidenreich, R.G., Krauter, J.G., Pietsch, J., 2002. Highly active palladium/activated carbon catalysts for Heck reactions: correlation of activity, catalyst properties, and Pd leaching. Chemistry 8, 622–631.

Please cite this article in press as: Bhavani, S. et al., Ultrasound assisted Mizoroki–Heck reaction catalyzed by Pd/C: Synthesis of 3-vinyl indoles as potential cytotoxic agents. Arabian Journal of Chemistry (2016), http://dx.doi.org/10.1016/j.arabjc.2016.02.002

Köhler, K., Heidenreich, R.G., Soomro, S.S., Pröckl, S.S., 2008. Supported palladium catalysts for Suzuki reactions: structure–property relationships, optimized reaction protocol and control of palladium leaching. Adv. Synth. Catal. 350, 2930–2936.

Lambert, J.D., Porter, Q.N., 1981. Vinylindenes and some heteroanalogues in the Diels-Alder reaction. VIII. 1-Benzyl-3-vinylindole as a diene. Aust. J. Chem. 34, 1483–1490.

Lopez-Alvarado, P., Steinhoff, J., Miranda, S., Avendano, C., Carlos Menendez, C., 2009. Efficient, one-pot transformation of indoles into functionalized oxindole and spirooxindole systems under Swern conditions. Tetrahedron 65, 1660–1672.

López, S., Rodríguez, V., Montenegro, J., Saá, C., Alvarez, R., Silva López, C., de Lera, A.R., Simón, R., Lazarova, T., Padrós, E., 2005. Synthesis of *N*-heteroaryl retinals and their artificial bacteriorhodopsins. ChemBioChem 6, 2078–2087.

Luche, J.-L., 1998. Synthetic Organic Sonochemistry. Plenum Press, New York.

Mason, T.J., 1997. Ultrasound in synthetic organic chemistry. Chem. Soc. Rev. 26, 443–451.

Mizoroki, T., Mori, K., Ozaki, A., 1971. Arylation of olefin with aryl iodide catalyzed by palladium. Bull. Chem. Soc. Jpn. 44, 581.

Nakhi, A., Prasad, B., Rao, R.M., Reddy, U., Sandra, S., Kapavarapu, R., Rambabu, D., Krishna, G.R., Reddy, C.M., Kishore, R., Misra, P., Iqbal, J., Pal, M., 2011. A new route to indoles via *in situ* desilylation-Sonogashira strategy: identification of novel small molecules as potential anti tuberculosis agents. Med. Chem. Commun. 2, 1006–1010.

Osanai, K., Yokoyama, Y., Kondo, K., Murakami, Y., 1999. Total synthesis of optically active costaclavine (synthetic studies of indoles and related compounds part 48). Chem. Pharm. Bull. 47, 1587–1590.

Order, R.B.V., Lindwall, H.G., 1945. 3-Indole aldehyde and certain of its condensation products. J. Org. Chem. 10, 128–133.

Pindur, U., Pfeuffer, L., 1989. Wittig-Olefinierung zu neuen donor- und akzeptor-substituierten 3-Vinylindolen: Optimierte Syntheseverfahren. Monatshefte fuer Chemie 120, 157–162.

Pindur, U., Lutz, G., Rogge, M., 1995. First synthesis of chiral 3-vinylindoles as 4π-components for diels-alder reactions. J. Heterocyclic Chem. 32, 201–206.

Pindur, U., Pfeuffer, L., Kim, M.-H., 1989. Locoselective [4 + 2] cycloadditions of vinylindoles with inverse electron demand: a new access of indolyl-substituted and annellated pyridazines. Helv. Chim. Acta 72, 65–72.

Pindur, U., Otto, C., 1992. A new access to 2′-amino-substituted vinylindoles as donor-activated heterocyclic dienes and their first diels-alder reactions. Tetrahedron 48, 3515–3526.

Pindur, U., Kim, M.H., Rogge, M., Massa, W., Molinier, M., 1992. New Diels–Alder reactions of (E/Z)-2′-methoxy-substituted 3-vinylindoles with carbo- and heterodienophiles: regio- and stereoselective access to [b]-annelated indoles and functionalized or [a]-annelated carbazoles. J. Org. Chem. 57, 910–915.

Pal, M., Dakarapu, R., Padakanti, S., 2004a. A direct access to 3-(2-oxoalkyl)indoles *via* aluminium chloride induced C–C bond formation. J. Org. Chem. 69, 2913–2916.

Pal, M., Venkataraman, S., Batchu, V.R., Dager, I., 2004b. Synthesis of 2-substituted indoles via Pd/C catalyzed reaction in water. Synlett, 1965–1969.

Pal, M., 2009. Palladium-catalyzed alkynylation of aryl and hetaryl halides: a journey from conventional palladium complexes or salts to palladium/carbon. Synlett, 2896–2912.

Palmisano, G., Bonrath, W., Boffa, L., Garella, D., Barge, A., Cravotto, G., 2007. Heck reactions with very low ligandless catalyst loads accelerated by microwaves or simultaneous microwaves/ultrasound irradiation. Adv. Synth. Catal. 349, 2338–2344.

Papamichael, D., 1999. The use of thymidylate synthase inhibitors in the treatment of advanced colorectal cancer: current status. Oncologist 4, 478–487.

Perosa, A., Tundo, P., Selva, M., Zinovyev, S., Testa, A., 2004. Heck reaction catalyzed by Pd/C, in a triphasic—organic/Aliquat 336/aqueous—solvent system. Org. Biomol. Chem. 2, 2249–2252.

Rambabu, D., Bhavani, S., Swamy, N.K., Rao, M.V.B., Pal, M., 2013. Pd/C-mediated depropargylation of propargyl ethers/amines in water. Tetrahedron Lett. 54, 1169–1173.

Rao, R.M., Reddy CH, U., Nakhi, A., Mulakayala, N., Alvala, M., Arunasree, M.K., Poondra, R.R., Iqbal, J., Pal, M., 2011. Sequential coupling/desilylation-coupling/cyclization in a single pot under Pd/C-Cu catalysis: Synthesis of 2-(hetero)aryl indoles. Org. Biomol. Chem. 9, 3808–3816.

Rubinstein, L.V., Shoemaker, R.H., Paull, K.D., Simon, R.M., Tosini, S., Skehan, P., Scudiero, D.A., Monks, A., Boyd, M.R., 1990. Comparison of in vitro anticancer-drug-screening data generated with a tetrazolium assay versus a protein assay against a diverse panel of human tumor cell lines. J. Natl. Cancer Inst. 82, 1113–1118.

Rao, K.N., Bhattacharya, R.K., Venkatachalam, S.R., 1998. Thymidylate synthase activity in leukocytes from patients with chronic myelocytic leukemia and acute lymphocytic leukemia and its inhibition by phenanthroindolizidine alkaloids pergularinine and tylophorinidine. Cancer Lett. 128, 183–188.

Reimann, S., Stötzel, J., Frahm, R., Kleist, W., Grunwaldt, J.-D., Baiker, A., 2011. Identification of the active species generated from supported Pd catalysts in heck reactions: an in situ quick scanning EXAFS investigation. J. Am. Chem. Soc. 133, 3921–3930.

Sharma, V., Kumar, P., Pathak, D., 2010. Biological importance of the indole nucleus in recent years: a comprehensive review. J. Heterocyclic Chem. 47, 491–502.

Šíša, M., Pla, D., Altuna, M., Francesch, A., Cuevas, C., Albericio, F., Álvarez, M., 2009. Total synthesis and antiproliferative activity screening of (±)-aplicyanins A, B and E and related analogues. J. Med. Chem. 52, 6217–6223.

Salter, M., Hazelwood, R., Pogson, C.I., Iyer, R., Madge, D.J., 1995. The effects of a novel and selective inhibitor of tryptophan 2,3-dioxygenase on tryptophan and serotonin metabolism in the rat. Biochem. Pharmacol. 49, 1435–1442.

Su, T., Han, X., Lu, X., 2014. Palladium(II)-catalyzed oxidative annulation of alkenylindoles with alkynes initiated by C–H activation. Tetrahedron Lett. 55, 27–30.

Sodeoka, M., Kato, M., Asakai, R., 2003. Indolylpyrrole derivatives and cell death inhibitors. US patent application no US 2003/0087949 A1, May 8.

Sala, G.D., Izzo, I., Aldo, S., 2006. A Pd-mediated approach to the synthesis of an unusual b-hydroxytryptophan amino acid constituent of cyclomarin A. Synlett, 1319–1322.

Suslick, K.S., Flannigan, D.J., 2008. Inside a collapsing bubble: sonoluminescence and the conditions during cavitation. Annu. Rev. Phys. Chem. 59, 659–683.

Skehan, P., Storeng, R., Scudiero, D., Monks, A., McMahon, J., Vistica, D., Warren, J.T., Bokesch, H., Kenney, S., Boyd, M.R., 1990. New colorimetric cytotoxicity assay for anticancer-drug screening. J. Natl. Cancer Inst. 82, 1107–1112.

Tao, Y., Zhang, F., Tang, C.-Y., Wu, X.-Y., Sha, F., 2014. Direct assembly of benzo[a]carbazole-5-carboxylates via a diels-alder reaction with arynes and 3-alkenylindoles. Asian J. Org. Chem. 3, 1292–1301. http://dx.doi.org/10.1002/ajoc.201402152.

Tsuji, J., 1995. Palladium Reagents and Catalysts. Wiley, New York, pp. 125–168.

Tan, B., Hernández-Torres, G., Barbas III, C.F., 2011. Highly efficient hydrogen-bonding catalysis of the Diels–Alder reaction of 3-vinylindoles and methyleneindolinones provides carbazole-spirooxindole skeletons. J. Am. Chem. Soc. 133, 12354–12357.

Vasseur, A., Harakat, D., Muzart, J., Le Bras, J., 2013. Aerobic dehydrogenative heck reactions of heterocycles with styrenes: a negative effect of metallic Co-oxidants. Adv. Synth. Catal. 355, 59–67.

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Verma, A.K., Danodia, A.K., Saunthwal, R.K., Patel, M., Choudhary, D., 2015. Palladium-catalyzed triple successive C–H functionalization: direct synthesis of functionalized carbazoles from indoles. Org. Lett. 17, 3658–3661.

Xie, X., Lu, J., Chen, B., Han, J., She, X., Pan, X., 2004. Pd/C-catalyzed Heck reaction in ionic liquid accelerated by microwave heating. Tetrahedron Lett. 45, 809–811.

Yokoyama, Y., Matsumoto, T., Murakami, Y., 1995. Optically active total synthesis of clavicipitic acid. J. Org. Chem. 60, 1486–1487.

Yahiaoui, S., Fardost, A., Trejos, A., Larhed, M., 2011. Chelation-mediated palladium(II)-catalyzed domino Heck−Mizoroki/Suzuki−Miyaura reactions using arylboronic acids: increasing scope and mechanistic understanding. J. Org. Chem. 76, 2433–2438.

Zhang, H.-H., Sun, X.-X., Liang, J., Wang, Y.-M., Zhao, C.-C., Shi, F., 2014. Catalytic asymmetric Povarov reaction of isatin-derived 2-azadienes with 3-vinylindoles. Org. Biomol. Chem. 12, 9539–9546.

Zheng, H., Liu, X., Xu, C., Xia, Y., Lin, L., Feng, X., 2015. Regio- and enantioselective Aza-Diels-Alder reactions of 3-vinylindoles: a concise synthesis of the antimalarial spiroindolone NITD609. Angew. Chem. Int. Ed. 54, 10958–10962.

Zheng, H., He, P., Liu, Y., Zhang, Y., Liu, X., Lin, L., Feng, X., 2014. Efficient synthesis of carbazolespirooxindole skeletons via asymmetric Diels–Alder reaction of 3-vinylindoles and methyleneindolinones. Chem. Commun. 50, 8794–8796.

Zhang, Z., Zha, Z., Gan, C., Pan, C., Zhou, Y., Zhiyong Wang, Z., Zhou, M.-M., 2006. Catalysis and regioselectivity of the aqueous Heck reaction by Pd(0) nanoparticles under ultrasonic irradiation. J. Org. Chem. 71, 4339–4342.

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