Synthesis of Indanones via Intramolecular Heck Reaction of Baylis-Hillman Adducts of 2-Iodobenzaldehyde

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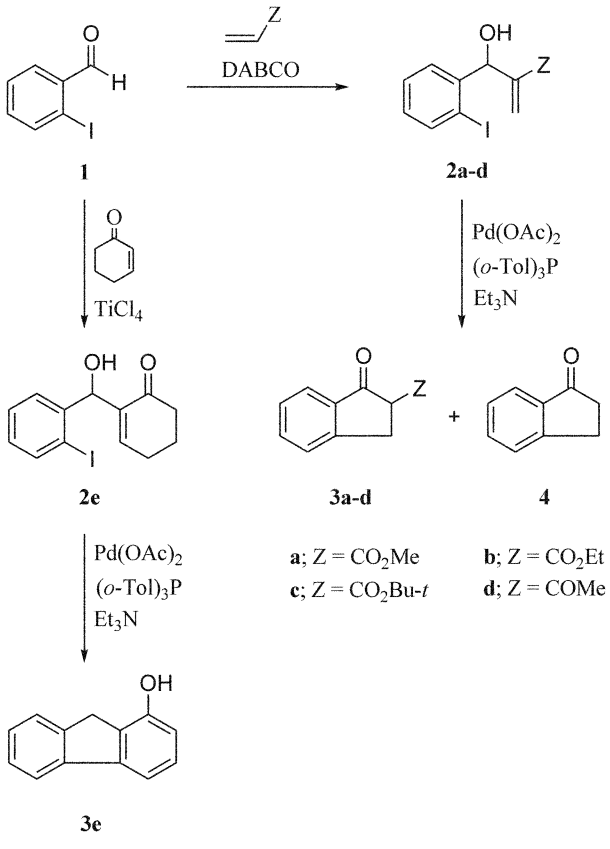
2-Carboalkoxy- and 2-acetyl-1-indanones are important building blocks in the synthesis of many natural products[1] and considerable efforts have been made to find selective routes to these compounds[2] including methylenation of aromatic 1,3-dicarbonyl compounds with the $MeOCH_2$-$COCl{\cdot}AlCl_3$ reagent[3] and tandem Knoevenagel condensation-cycloalkylation of aromatic 1,3-dicarbonyl compounds and aldehydes in the presence of Lewis acid.[4]

Over the last decade palladium-catalyzed reactions have emerged as extremely versatile methods for the synthesis of highly complex carbo- and heterocyclic synthesis.[5] The coupling of vinyl or aryl halides, triflates or similar intermediates with alkenes under palladium (0) catalysis is known as the Heck reaction and both its inter- and intramolecular versions are powerful tools in organic synthesis.[6] Among them, the intramolecular Heck reaction on substrates possessing an allylic alcohol moiety have been recently studied.[7] This methodology provides a good approach to a wide variety of carbo- or heterocycles having carbonyl group.

As part of our ongoing interest in Baylis-Hillman (BH) reaction,[8] particularly for the construction of heterocycles[9] and isomerization of BH acetates,[10] we decided to investigate the intramolecular Heck reaction of BH adducts[11] of 2-iodobenzaldehyde. The similar example of this kind described in the literature is the transformation of 1-(2-bromophenyl)-2-octen-1-ol into 3-pentylindanone in moderate yield.[7]

The reaction of 2-iodobenzaldehyde (**1**) with methyl acrylate in the presence of 1 equivalent of 1,4-diazabicyclo[2,2,2]octane (DABCO) in neat at room temperature afforded BH adduct methyl 3-hydroxy-3-(2-iodophenyl)-2-methylenepropanoate (**2a**) in 95% yield. Similarly, the treatment of **1** with ethyl acrylate, *tert*-butyl acrylate and methyl vinyl ketone gave the corresponding BH adducts **2b-d** in 58-86% yields. In the case of cyclohexenone BH adduct **2e** was obtained using $TiCl_4$[12] instead of DABCO in 64% yield. With BH adducts **2a-e** in hand, we then turned our attention to the Pd-catalyzed annulation reaction. Our first choice of reaction conditions for the intramolecular Heck reaction with **2a** included the use of 5 mol% palladium acetate as catalyst, acetonitrile as solvent, tri-*o*-tolylphosphine (20 mol%) and triethylamine (3 equiv.) as a base. Under these conditions, a reaction ensured upon heating at 80 °C under an inert atmosphere and 2-carbomethoxy-1-indanone **3a** and decarboxylated product indanone (**4**) were isolated in 34 and 10% yields after column chromatography.[13] Reaction of **2b** under similar conditions provided a mixture of **3b** (32%) and **4** (9%). However, when **2c** was reacted at the same conditions, indanone **4** (39%) was obtained as a major compound and 2-*tert*-carbobutoxy-1-indanone (**3c**) (27%) as a minor one. This kind of decarboalkoxylation of β-keto esters under Heck reaction conditions are well known in the literature.[11b] Similarly **2d** gave an 2-acetyl-1-indanone (**3d**) in 35% yield (Scheme 1, Table 1). Interestingly, in the case of **2e**, the reaction produced the 32% yield of 1-hydroxyfluorene (**3e**). In general, the conversion yields are low to moderate ranging from 32 to 66% and indanones **3** exist mostly in enol-keto tautomer mixtures.



Scheme 1

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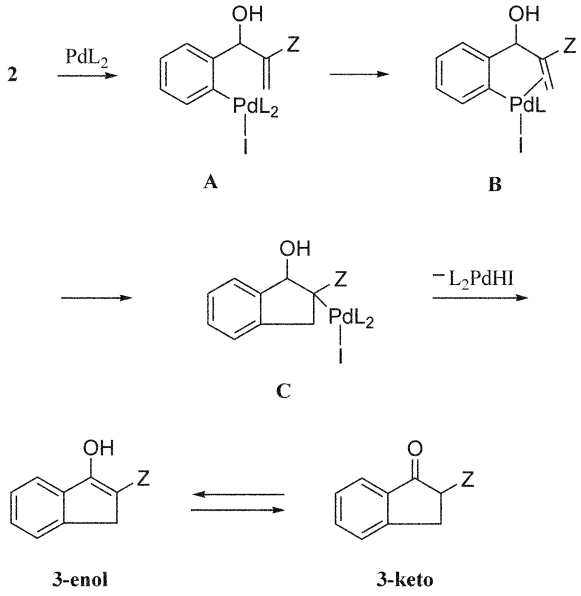
Table 1. Synthesis and Intramolecular Heck Reaction of Baylis-Hillman Adducts **2**

Entry	Olefins	Time (h)[a]	Product (% yield)	Time (h)[b]	Product (% yield)
1	CO_2Me	72	**2a** (95)	18	**3a**/**4** (34/10)
2	CO_2Et	80	**2b** (86)	18	**3b**/**4** (32/9)
3	CO_2Bu-*t*	96	**2c** (58)	2	**3c**/**4** (27/39)
4	COMe	168	**2d** (65)	12	**3d** (35)
5	=O	2	**2e** (64)	6	**3e** (32)

[a]Reaction time of Baylis-Hillman reaction. [b]Reaction time of intramolecular Heck reaction.



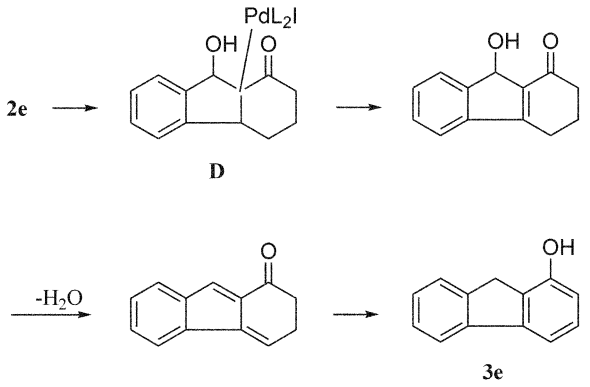
Scheme 2

The mechanism involves the oxidative addition of the iodide resulting in a palladium (II) complex (**A**). An alkene in the reacting system will lead to coordination (**B**) followed by migratory insertion into the palladium-carbon σ bond (**C**). Palladium is expelled from the molecule by a β-hydride elimination reaction and the product is an enol, then tautomerized to the ketone. A base then regenerates the palladium (0) catalyst (Scheme 2). Formation of **3e** can be presumably explained by an elimination of the other β-hydrogen in the alkyl palladium intermediate (**D**) followed by loss of water and aromatization by proton migration as depicted in Scheme 3.

In summary, although the synthetic yields are low, we have shown a simple, two step synthesis of indanone derivatives using Baylis-Hillman and Heck reactions.

Experimental Section

General Procedure for the Preparation of Baylis-Hillman Adducts 2a-d. To a stirred solution of 2-iodobenzaldehyde **1** (1.16 g, 5 mmol) in THF (10 mL) was added acrylate (15 mmol) or methyl vinyl ketone (7.5 mmol) and DABCO (0.56 g, 5 mmol) at r.t. After stirring at r.t. for the period mentioned in Table 1, the reaction mixture was diluted with water (20 mL) and extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was evaporated *in vacuo*. The products were separated by column chromatography over silica gel (100-200 mesh) using hexane/EtOAc (8 : 1) as eluant and were characterized through spectral studies.



Scheme 3

Methyl 3-Hydroxy-3-(2-iodophenyl)-2-methylenepropanoate (2a). Colorless oil. Yield: 1.51 g (95%); IR (neat): 3416, 1711, 1630 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.17 (d, 1 H, J = 4.3 Hz), 3.79 (s, 3H), 5.55 (s, 1H), 5.80 (d, 1H, J = 4.0 Hz), 6.36 (s, 1H), 6.98-7.04 (m, 1H), 7.36-7.52 (m, 2H), 7.82-7.85 (m, 1H); MS: m/z (%) 318 (M^+, 10), 300 (8), 191 (100), 174 (46), 131 (21).

Ethyl 3-Hydroxy-3-(2-iodophenyl)-2-methylenepropanoate (2b). Colorless oil. Yield: 1.46 g (86%); IR (neat): 3414, 1711, 1635, 1619 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.28 (t, 3 H, J = 7.3 Hz), 3.19 (d, 1H, J = 4.3 Hz), 4.23 (q, 2H, J = 7.3 Hz), 5.56 (s, 1H), 5.80 (d, 1H, J = 4.0 Hz), 6.37 (s, 1H), 6.98-7.04 (m, 1H), 7.35-7.83 (m, 2H), 7.85-7.86 (m, 1H); MS: m/z (%) 332 (M^+, 4), 315 (6), 231 (30), 205 (100), 177 (62), 159 (35), 131 (19).

***tert*-Butyl 3-Hydroxy-3-(2-iodophenyl)-2-methylenepropanoate (2c).** Colorless oil. Yield: 1.04 g (58%); IR (neat): 3436, 1712, 1634 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.44 (s, 9H), 3.09 (d, 1H, J = 4.0 Hz), 5.51 (d, 1H, J = 1.1 Hz), 5.73 (d, 1H, J = 4.0 Hz), 6.28 (d, 1H, J = 1.1 Hz), 6.97-7.01 (m, 1H), 7.33-7.46 (m, 2H), 7.81-7.83 (m, 1H); MS: m/z (%) 360 (M^+, 15), 305 (20), 287 (16), 233 (24), 189 (100), 177 (69), 115 (56).

4-Hydroxy-4-(2-iodophenyl)-3-methylenebutan-2-one (2d). Colorless oil. Yield: 0.98 g (65%); IR (neat): 3409, 1677, 1627 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.42 (s, 3H), 3.31 (d, 1H, J = 4.0 Hz), 5.61 (s, 1H), 5.80 (d, 1H, J = 3.7 Hz), 6.19 (s, 1H), 6.98-7.04 (m, 1H), 7.37-7.55 (m, 2H), 7.82-7.85 (m, 1H); MS: m/z (%) 302 (M^+, 15), 301 (39), 175 (100), 158 (56).

(2-Iodophenyl)hydroxymethyl-2-cyclohexen-1-one (2e).[12] Into a dry vial was added 2-iodobenzaldehyde **1** (1.16 g, 5 mmol), 2-cyclohexen-1-one (0.19 g, 2.0 mmol) and CH_2Cl_2 (1.5 mL). The reaction vial was immersed in a 0 °C bath, and $TiCl_4$ (1.2 mL, 1.0 M in CH_2Cl_2, 1.2 mmol) was then added dropwise. The resulting solution was stirred at 0 °C for 10 min. and at r.t. for 2 h. The reaction was quenched by saturated aq. $NaHCO_3$ solution (3.0 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated to dryness. Purification by flash chromatography using hexane/EtOAc (8 : 1) as eluant provided 1.03 g (64%) of **2e** as a colorless oil. IR (neat): 3417, 1704, 1669 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.00-2.07 (m, 2H), 2.32-2.36 (m, 2H), 2.51-2.56 (m, 2H), 3.56 (d, 1H, J = 3.6 Hz), 5.77 (d, 1H, J = 3.6 Hz), 6.39 (t, 1H, J = 4.2 Hz), 6.99-7.04 (m, 1H), 7.39-7.44 (m, 1H), 7.57-7.60 (m, 1H), 7.81-7.83 (m, 1H); MS: m/z (%) 328 (M^+, 4), 327 (23), 201 (14), 200 (42), 185 (100), 183 (85),123 (38).

General Procedure for Intramolecular Heck Reaction of Baylis-Hillman Adducts. Synthesis of 1-Indanones 3 and 4: A typical reaction procedure involved heating a mixture of Baylis-Hillman adduct **2** (2 mmol), $Pd(OAc)_2$ (22.45 mg, 0.1 mmol), P(*o*-tol)$_3$ (0.12 g, 0.4 mmol) and Et_3N (0.61 g, 6.0 mmol) in CH_3CN (10 mL) under N_2 atmosphere for the period mentioned in Table 1. The reaction mixture was extracted with EtOAc, washed with dilute HCl (10%, 5 mL), water, brine and finally dried over anhydrous $MgSO_4$. The products were separated by column chromatography over silica gel (100-200 mesh) using hexane/EtOAc (7 : 1) as eluant and were characterized through spectral studies compared with literature values.

2-Carbomethoxy-1-indanone (3a) and 1-Indanone (4). For **3a**: White solid. Yield: 34%; mp 59-60 °C (lit.[14] 59.8-60.1 °C); IR (KBr): 3462, 1735, 1711 cm^{-1}; ^1H NMR ($CDCl_3$): keto-enol (85-15%), δ 3.38 (dd, 0.85 × 1H, J = 17.4 and 8.2 Hz, ketonic H-3), 3.52 (s, 0.15 × 2H, enolic H-3), 3.58 (dd, 0.85 × 1H, ketonic H-3, J = 17.4 and 4.3 Hz), 3.75 (dd, 0.85 × 1H, J = 8.2 and 4.3 Hz, ketonic H-2), 3.80 (s, 0.85 × 3H, ketonic CH_3), 3.86 (s, 0.15 × 3H, enolic CH_3), 7.38-7.80 (m, 4H); MS: m/z (%) 190 (M^+, 44), 159 (15), 158 (28), 130 (100), 77 (14).

For **4**: White solid. Yield: 10%; mp 40-42 °C (lit.[15] 42 °C); IR (KBr) 1707, 1609 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.70 (dd, 2H, J = 6.1 and 5.8 Hz), 3.16 (dd, 2H, J = 6.1 and 5.8 Hz), 7.36-7.78 (m, 4H); MS: m/z (%) 133 (71), 132 (M^+, 100), 104 (42), 78 (36).

2-Carboethoxy-1-indanone (3b)[4] **and 1-Indanone (4).** For **3b**: An oil. Yield: 32%; IR (neat): 3414, 1740, 1712 cm^{-1}; ^1H NMR ($CDCl_3$) : keto-enol (84-16%), δ 1.31 (t, 0.84 × 3H, J = 7.0 Hz, ketonic CH_3), 1.37 (t, 0.16 × 3H, J = 7.0 Hz, enolic CH_3), 3.37 (dd, 0.84 × 1H, J = 17.4 and 8.2 Hz, ketonic H-3), 3.51 (s, 0.16 × 2H, enolic H-2), 3.56 (dd, 0.84 × 1H, J = 17.4 and 4.0 Hz, ketonic H-3), 3.72 (dd, 0.84 × 1 H, J = 8.2 and 4.0 Hz, ketonic H-2), 4.25 (q, 0.84 × 2H, J = 7.0 Hz, ketonic CH_2), 4.32 (q, 0.16 × 2H, J = 7.0 Hz, enolic CH_2), 7.37-7.78 (m, 4H); MS: m/z (%) 204 (M^+, 85), 159 (24), 158 (35), 130 (100), 103 (44), 77 (19).

For **4**: Yield: 9%.

2-*tert*-Carbobutoxy-1-indanone (3c) and 1-Indanone (4). For **3c**: Colorless solid. Yield: 27%; mp 44-45 °C (lit.[16] 44-46 °C); IR (KBr): 1731, 1711 cm^{-1}; ^1H NMR ($CDCl_3$): keto-enol (100-0%), δ 1.49 (s, 9H), 3.32 (dd, 1H, J = 17.2 and 8.4 Hz), 3.48 (dd, 1H, J = 17.2 and 4.0 Hz), 3.61 (dd, 1H, J = 8.4 and 4.0 Hz), 7.34-7.74 (m, 4H).

For **4**: Yield: 39%.

2-Acetyl-1-indanone (3d). White solid; Yield: 35%; mp 73-75 °C (lit.[17] 75-76 °C); IR (KBr): 3460, 1715, 1695, 1658, 1605 cm^{-1}; ^1H NMR ($CDCl_3$): keto-enol (15-85%), δ 2.18 (s, 0.85 × 3H, enolic CH_3), 2.50 (s, 0.15 × 3H, ketonic CH_3), 3.13 (dd, 0.15 × 1H, J = 17.4 and 7.9 Hz, ketonic H-3), 3.59 (s, 0.85 × 2H, enolic H-3), 3.97 (dd, 0.15 × 1H, J = 7.9 and 3.0 Hz, ketonic H-2), 3.74 (dd, 0.15 × 1H, J = 17.4 and 3.0 Hz, ketonic H-3), 7.31-7.83 (m, 4H), 11.80 (s, 0.85 × 1H); MS: m/z (%) 174 (M^+, 21), 131 (100), 103 (42), 77 (24).

Synthesis of 1-Hydroxyfluorene (3e). The procedure was the same as described in the preparation of 1-indanone **3a-d** using **2e**. Yield 32%; yellow solid; mp 118-119 °C (lit.[18] 120 °C); IR (KBr): 3517, 1585 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.85 (s, 2H), 4.84 (br s, 1H), 6.76 (d, 1H, J = 8.1 Hz), 7.26-7.42 (m, 4H), 7.57 (d, 1H, J = 7.3 Hz), 7.77 (d, 1H, J = 7.3 Hz); MS: m/z (%) 182 (M^+, 100), 165 (12), 152 (38).

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