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 products¹ and considerable efforts have been made to find selective routes to these compounds² including methylenation of aromatic 1,3-dicarbonyl compounds with the MeOCH₂-COCl·AlCl₃ reagent³ and tandem Knoevenagel condensationcycloalkylation 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 heterocycles⁹ and isomerization of BH acetates,¹⁰ we decided to investigate the intramolecular Heck reaction of BH adducts¹¹ 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)-2methylenepropanoate (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 TiCl412 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-1indanone 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-1indanone (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 2acetyl-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)"	Product (% yield)	Time (h) ⁶	Product (% yield)
1	CO ₂ Me	72	2a (95)	18	3a/4 (34/10)
2	CO2Et	80	2b (86)	18	3b/4 (32/9)
3	CO ₂ Bu- <i>t</i>	96	2c (58)	2	3c/4 (27/39)
4	СОМе	168	2d (65)	12	3d (35)
5	◯=o	2	2e (64)	6	3e (32)

"Reaction time of Baylis-Hillman reaction, "Reaction time of intramolecular Heck reaction



The mechanism involves the oxidative addition of the iodide resulting in a palladium (11) 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 \times 20 mL). The combined organic layers were dried over anhydrous MgSO4 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.

Methyl 3-Hvdroxy-3-(2-iodophenyl)-2-methylenepropanoate (2a). Colorless oil. Yield: 1.51 g (95%); IR (neat): 3416, 1711, 1630 cm⁻¹; ¹H NMR (CDCl₃): δ 3.17 (d, 1 H, J = 4.3 Hz), 3.79 (s, 3H), 5.55 (s, 1H), 5.80 (d, 1H, J = 4.0Hz), 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 (CDCl₃): 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 (CDCl₃): 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 (CDCl₃): 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).

Notes

Notes

(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 CH₂Cl₂ (1.5 mL). The reaction vial was immersed in a 0 °C bath, and TiCl₄ (1.2 mL, 1.0 M in CH₂Cl₂, 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. NaHCO₃ solution (3.0 mL). The phases were separated, and the aqueous phase was extracted with EtOAc $(3 \times 10 \text{ mL})$. The combined organic layers were washed with water and brine, dried over anhydrous MgSO4, 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 (CDCl₃): 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 CH₃CN (10 mL) under N₂ 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 MgSO₄. 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 (CDCl₃): 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 CH₃), 3.86 (s, 0.15 × 3H, enolic CH₃), 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 (CDCl₃): 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 (CDCl₃) : keto-enol (84-16%), δ 1.31 (t. 0.84 × 3H, J = 7.0 Hz, ketonic CH₃), 1.37 (t. 0.16 × 3H, J = 7.0 Hz, enolic CH₃), 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 CH₂), 4.32 (q, 0.16 × 2H, J = 7.0 Hz, enolic CH₂), 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 (CDCl₃): 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 (CDCl₃): keto-enol (15-85%). δ 2.18 (s. 0.85 × 3H. enolic CH₃), 2.50 (s. 0.15 × 3H, ketonic CH₃), 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 = 17.4 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 (CDCl₃): 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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